Synthesis and evaluation of some poly(lactide-co-glycolides) for use in sustained release tablets.

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SYNTHESIS AND EVALUATION OF SOME POLY(LACTIDE-CO-GLYCOLIDES) FOR USE IN SUSTAINED RELEASE TABLETS

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ABSTRACT

The use of biodegradable polymers makes the surgical removal of the depleted device unnecessary. Furthermore the degradation of carrier can be utilized to control the rate of drug release. The biodegradable polymers receiving the most attention at this time are these prepared from lactic and glycolic acids, mainly because of the established biocompatibility.

The synthesis of poly(lactide-co-glycolide) polymers by the ring opening polymerization of lactide and glycolide was investigated from a pharmaceutical viewpoint. The effects of changing the polymerization conditions on the properties of the resulting polymer and on the yield of the polymerization were discussed with respect to a co-ordinate mechanism of polymerization. The factors investigated were the catalyst type and concentration, co-catalyst concentration and time and temperature of polymerization. The polymerization conditions affected the properties of the resulting polymers through their effect on polymer mw and composition. There was significant interdependence between the preparative variables. It appears possible to control the properties of the polymer formed by modifying the polymerization conditions.

A spray dried technique was adopted to prepare polymer powders. The main problem encountered in the spray drying was the production of threads, instead of particles, when relatively high molecular weight (MW) polymers were

sprayed, unless very dilute solutions were used. The spray dried powders were soft and ductile having yield pressure ranging from 28 to 33 MPa. The degradation of spray dried powders proceeded through a non autocatalytic mechanism in phosphate buffer, pH = 7.4. The rate of hydrolysis, and consequently the rate of mass loss from the polymer increased with an increase in glycolide content or a decrease in the polymer MW.

The contact angle of spray dried polymers with water ranged from 72^{o} to 78^{o}, indicating a moderate polymer hydrophobicity. The percent water uptake, water uptake rate and swelling of the polymers increased with increasing glycolide content or decreasing polymer MW.

The rate of phenobarbitone (model drug) release from polylactide co-glycolide) heterogeneous matrices was affected by both technological factors and polymer properties. A composite release mechanism was considered to operate involving diffusion of the drug through water filled capillaries and pores of the matrix and drug diffusion through the swollen polymer. The release of phenobarbitone was significantly sustained, indicating the suitability of using poly(lactide-co-glycolide) matrix tablets in long-term controlled drug delivery.

CONTENTS

1. GENERAL INTRODUCTION

1.1 Biodegradable Polymers in Controlled Drug Delivery

1.1.1 Introduction

The use of biodegradable polymers in the formulation of controlled drug release systems makes the surgical removal of the depleted device unnecessary. In addition, the degradation process can be utilized to control the rate of drug release.

Terminology for this process has tended to be unprecise with biodegradation bioerosion and bioabsorption used to describe *in vivo* degradation phenomena. The term bioabsorbable has been used to characterize surgical sutures which are 'absorbed' by the body, i.e. the solid material eventually disappears from the site of application.

No clear definitions have been made between the terms biodegradation and bioerosion. Graham and Wood (1982) and Heller (1985) used 'biodegradable" and "bioerodible" respectively to describe polymers completely solubilizing as a consequence of a degradation process and ultimately disappearing from the site of implantation. However, Holland *et al.* (1986) took the term biodegradation to refer to the hydrolytic, enzymatic or bacteriological degradation processes occurring in a polymer, which do not necessarily proceed to a stage where the physical form of the polymer is affected. Bioerosion, on the other hand, necessitates physical loss from the polymer matrix and this may be

brought about by a variety of physical or chemical processes which are not always specified.

1.1.2 Biodegradation Mechanisms

Polymer degradation can be classified by three basic mechanisms (fig 1). Type I degradation refers to the polymers soluble in water, which have been made insoluble by covalent cross-links and which solubilize as the cross-links (type IA) or the backbone (type IB) undergo hydrolytic cleavage. In type II degradation, polymers that are initially water-insoluble are solubilized by hydrolysis, ionization, or protonation of a pendant group. In type III degradation, hydrophobic polymers are converted to small water-soluble molecules by backbone cleavage. These types represent extreme cases and actual degradation may take place by a combination of all three types. (Heller, 1985).

1.1.3 Drug Release From Biodegradable Delivery Systems

The rate of drug release from biodegradable reservoir devices can be constant and predictable, provided the rate controlling membrane does not degrade until drug delivery has been completed. In this case the kinetic models for the release from non-biodegradable reservoir devices (Baker and Lonsdale, 1974) are applicable. The rate of release can be controlled only by changing the shape and dimensions of the device, or by changing the nature or thickness of the membrane; degradation simply removes the expended

device. If the rate controlling membrane undergoes significant degradation during drug delivery, changes in membrane thickness or physical properties would change the rate of drug release.

Drug release from biodegradable monolithic devices may predominantly occur by diffusion, degradation of the polymer, or by a combination of these two mechanisms. If the matrix degrades much slower than the drug diffuses, the release kinetics can be described by the Higuchi's model (Higuchi, 1963). If the drug release due to diffusion is minimal, whilst degradation is relatively rapid, then the rate of drug release can be controlled by degradation.

There are two types of hydrolytic degradation of a solid polymer. In one, homogeneous (usually referred to as "bulk") degradation the hydrolysis occurs throughout the matrix. In the other, heterogenous (usually referred to as "surface") degradation, the hydrolysis is confined to the surface of the device (Holland *et al.*, 1986).

The detailed understanding of drug release from a matrix undergoing homogeneous degradation is complex, because it combines diffusion and degradation. Because the homogenous degradation changes the matrix the permeability of the polymer to the drug will increase with time and the release rate will not normally be predictable. Theoretically, heterogeneously degraded matrices should not produce zero-order release kinetics. However, many do; probably because of some degree of tissue encapsulation, which occurs with

all dosage forms and leads to the formation of a water boundary layer capable of controlling release rates (Benagiano and Gabelnik, 1979).

The drug release from matrices undergoing heterogeneous degradation can be zero-order provided diffusional release is minimal and the overall surface area of the device remains constant. In addition, the deterioration of the mechanical properties, which can result in the disintegration of devices undergoing homogenous degradation, is avoided by utilizing devices which undergo surface degradation. (Heller, 1985).

Where the surface degradation follows zero-order kinetics the drug release can be determined by equation 1, proposed by (Hophenberg, 1976):

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{K_o t}{C_o \alpha}\right]^n \qquad \text{Equation 1}$$

Where Mt/M_∞ is the fraction of drug released at time t, K_o is the zero-order degradation rate constant, and C_o is the initial drug content. The values n and α depend on the geometry of the device. For the infinite slab, n=1 and α is half the thickness; for the cylinder n=2 and α is the radius; for the sphere, n=3 and α is the radius. It is evident that a constant rate of release is only obtained

from the infinite slab and that delivery rates from cylinders and spheres decrease with time.

1.2 Biodegradable Drug Delivery Systems

1.2.1 Delivery Systems Based on Polymers Undergoing Type I Degradation

In these systems water-soluble macromolecules are converted to an insoluble three dimensional network by means of covalent cross-links. When these networks are placed in an aqueous environment they can swell only to the extent allowed by the cross-link density. Such systems are completely permeated by water and the aqueous solubility of the incorporated drug becomes a very important consideration. Biodegradable hydrogels could be useful for extended delivery either of drugs with low solubility in water, or macromolecules physically entangled in the cross-linked hydrogel matrix. The latter cannot diffuse out of the matrix even though it is freely soluble in water.

Type I degradation can be subdivided into two subtypes, 1A and 1B.

In type 1A degradation the hydrogel dissolves when the cross-links, which connect the water-soluble polymer chains, cleave. The degradation products are high molecular weight (MW) polymers soluble in water and, if such systems are to be implanted, these polymers must degrade further to small water soluble molecules which can be readily eliminated from the implantation site.

A widely investigated system undergoing type IA degradation is that prepared by copolymerizing vinyl pyrrolidine or acylamide with N,N′ methylene-bisacrylamide. The rate of degradation is very slow and the hydrogel completely solubilizes with a useful time span at cross-linker concentration of less than 1% (Heller 1985).

Hydrogels from polyacrylamide or poly(vinyl pyrrolidine) cross-linked with N,N′ methylene bisacrylide have been investigated for the controlled release of macromolecules, such as bovine serum albumin, rabbit immunoglobulin, bovine pancreatic insulin, and rat luteinizing hormone. The results obtained show that these hydrogels release the macromolecules at satisfactory rates only at the high cross-link density necessary to immobilize the macromolecules which prevents solubilization of the matrix (Heller and Baker, 1980).

Another system of interest is gelatin cross-linked with formaldehyde. The hydrolytic instability of gelatin resides both in the cross-linkages and the poly(amino acid) backbone, so that it is suitable for both topical and systemic applications. Gelatin cross-linked with formaldehyde has been used as a matrix for the controlled release of hydrocortisone acetate and a useful prolonged release of the drug was achieved. The first order kinetics indicated that matrix erosion contributed little or nothing to the release of the drug and depletion occurred before significant matrix degradation (Heller, 1980).

In subtype 1B degradation the hydrogel dissolves by cleavage of the water-soluble polymer chains resulting in low MW degradation products. Thus, provided all degradation products are toxicologically innocuous, such systems can be considered for implantation applications.

Subtype 1B degradation is undergone by the polymer prepared by copolymerizing dextran, previously reacted with acrylic acid glycidyl ester, and N,N′-methylene bisacrylamide. Macromolecules such as carbonic anhydrase, human serum albumin, immunoglobulin, and catalase have been incorporated with microspheres from this material with no loss of activity *in vivo* degradation of these microspheres depended on enzymatic activity. Release of proteins from the polyacrylodextran particles was greater than from polyacrylamide particles (Edman *et al.*, 1980).

Hydrogels were prepared by copolymerizing fumaric acid and poly(ethylene glycol) and were cross-linked with various amounts of N-vinyl pyrrolidine. The release of bovine serum albumin from microspheres of this hydrogel was controlled by the degradation of the matrix and could be regulated by the amount of vinyl co-monomer used. The rate of degradation, and consequently the rate of drug release, could be increased by partial substitution of fumaric acid by a diacid containing and electron withdrawing group (Heller *et al.*, 1983).

1.2.2 Delivery Systems Based on Polymers Undergoing Type II Degradation

Two classes of devices using type II, or a combination of type II and III degradation, have been developed. In one the drug is dispersed within, or is surrounded by the polymer matrix being released as solubilization takes place. The other class contains the active agent covalently bonded to the polymer chain by a hydrolytically labile bond, so that the active agent is released to the surrounding medium as this bond cleaves (pendant chain systems).

Polymers of the first class are partially esterified copolymers of methyl vinyl ether and maleic anhydride, or partially esterified copolymers of ethylene and maleic anhydride (Heller *et al.*, 1978). They solubilize by ionization of carboxylic acid groups. In a constant pH environment they undergo a controlled dissolution process and matrices release the incorporated drug at a rate controlled by the surface degradation process. Disks from this material inserted in the lower fornical cul-de-sac of rabbits have been shown to release hydrocortisone at a constant rate (Heller and Baker, 1980).

The partial ester copolymer has also been used as a model for a self-regulated drug delivery system in which the drug release is mediated by the amount of a specific external molecule. Hydrocortisone loaded disks were coated with hydrogel containing urease. Hydrolysis of urease causes an increase in the pH, due to the release of ammonium ions,

which in turn increases both the degradation and hydrocortisone release rate (Heller and Trescony, 1979).

Both water soluble and water-insoluble biodegradable pendant chain systems have been investigated.

A significant feature of the soluble pendant chain systems is the ability to target drugs to specific body sites. Poly(l-glutamic acid), in which the homing group immunoglobulin and the anticancer agent p-phenylene diamine mustard have been covalently bonded, have been used to target lymphoma mice cells. The homing group enhances the effectiveness of the anticancer agent, presumably by concentrating the polymer at the lymphoma cells. The macromelecular drug was shown to be more effective than the individual component, or mixtures of the individual components (Rowland *et al.*, 1975).

In the water insoluble pendant chain systems, polymers initially soluble in water have been rendered insoluble by the covalent attachment of a hydrophobic drug. One such system has been prepared by coupling norethindrone to poly(N^5-hydroxypropyl-l-glutamine) via carbonate linkages. Upon implantation in rats, slowly declining release kinetics over 144 days were obtained. Only minor tissue reaction and no immunologic response was observed (Petersen *et al.*, 1980).

The release of drugs from insoluble pendant chain systems is considered to proceed via aqueous diffusion into the

polymer, hydrolysis of the polymer-drug linkages and diffusion of the drug from the matrix. The release rate is determined by a combination of the rate of hydrolysis and rate of water permeation into the polymer (Heller, 1985).

1.2.3 Delivery Systems Based on Polymers Undergoing Type III Degradation

In these systems, high molecular weight water insoluble macromolecules are converted to small, water-soluble molecules by hydrolytic cleavage of labile bonds in the polymer backbone. Because these polymers are converted to small, water-soluble molecules, their principal application is for the systemic administration of therapeutic agents from subcutaneous, intramuscular or intraperitoneal implantation sites.

Polymeric systems containing hydrolytic instability in the polymer backbone are: aliphatic polyesters, polyamides, poly(cyanoacrylates), polyanhydrides, poly(orthoesters) and polyphosphazenes.

1.2.3.1 Aliphatic Polyesters

1.2.3.1.1 Poly((ϵ-Caprolactone)

Poly(ϵ-caprolactone) is a semicrystalline polyester having glass transition temperature, T_g=65^{o}C and melting point 63^{o}C (Pitt *et al.* 1980). It is prepared by the ring opening polymerization of the ϵ-caprolactone which can be effected by at least four different mechanisms categorized as

anionic, cationic, co-ordination and radical. Each method provides different degrees of control of the MW and molecular weight distribution (MWD), the end group composition, and the chemical structure and sequence distribution of the poly(ϵ-caprolactone) copolymers. Each of these characteristics, in turn, affects the permeability and biodegradability of the polymer (Pitt, 1990a).

Poly(ϵ-caprolactone) biodegrades through an homogeneous biphasical process. Degradation begins with random hydrolytic scission of the ester bonds. This chain scission has been shown to be autocatalyzed by the generation of carboxylic acid end groups. There is no weight loss during this first stage of degradation. Second phase degradation is characterized by a decrease in the rate of chain scission and the onset of weight loss. Weight loss from the polymer was attributed to the diffusion out of the small chain segments produced by the break up of the polymer mass. The final products of poly(ϵ-caprolactone) metabolism are ϵ-hydroxycaproic acid and water (Pitt, 1990a).

Complete elimination from the body of the poly(ϵ-caprolactone) with an initial number average molecular weight, M_n, of 50,000 requires three years (Holland *et al.*, 1986). However, degradation can be accelerated to more useful rates by employing copolymers, or blends of poly(ϵ-caprolactone) with other biodegradable polymers (Pitt *et al.*, 1981b; Pitt *et al.* 1987).

Poly(ε-caprolactone) and its copolymers have been considered for the controlled delivery of drugs such as steroids, narcotic antagonists and macromolecules (Pitt and Schindler, 1984; Pitt *et al.*, 1987; Tice *et al*, 1987).

Release of lipophilic drugs from monolithic poly (ε-caprolactone) devices is very rapid and diffusion controlled, but can be slowed by employing copolymers of poly(ε-caprolactone) instead of the homopolymer. Thus, l-methadone was microencapsulated with poly(ε-caprolactone-co-l-lactide) using a solvent evaporation technique. Increasing the proportion of lactic acid slowed the rate of *in vitro* drug release whilst the release mechanism changed from diffusion to degradation controlled (Cha and Pitt, 1988).

Levonorgestrel when suspended in a suitable oil, such as ethyl oleate, and incorporated into poly (ε-caprolactone) capsules released the steroid at a constant rate for up to one year, when implanted in rabbits. The oil apparently served to enhance the contact and dissolution of the drug into the capsule wall (Pitt and Schindler, 1984).

Whereas poly (ε-caprolactone) is very permeable to low MW drugs, Fickian diffusion of macromolecules through poly (ε-caprolactone) membranes is too slow to have any practical application. This deficiency was recently overcome by preparing poly (ε-caprolactone) capsules with controlled porosity by a leaching procedure. Thus, a constant release rate of a luteinizing hormone releasing

hormone (LHRH) analogue was maintained for more than 60 days using this technique (Schindler, 1987).

The microencapsulation and controlled release of nucleic acids to stimulate the production of interferon has been patented (Tice *et al.*, 1987).

1.2.3.1.2. Poly(3-hydroxy butyric acid)

Poly(d(-) - 3 - hydroxybutyric acid) (PHB) has been obtained from strains of bacteria, such as *Azobacter beijeinckii, Bacillus megatenium, Rhodosririllum rubrum* and *Bacillus cereus* (Gilding, 1981; Korsatko *et al.*,1983a). Grassie *et al.* (1984) have described the synthetic preparation of low MW PHB.

The degradation of PHB appears to be a simple hydrolysis *in vitro*, but there are indications of enzymatic involvement *in vivo* (Holmes, 1985). The biodegradation rate of PHB and its valerate copolymers (PHB-PHV) has been shown to depend on the polymer MW, the porosity of the matrix, and the valerate content of the copolymer (Holland *et al.*, 1987). The polymers are regarded as non-toxic and the monomer is a normal constituent of human blood (Gould *et al.*, 1987),

Pouton *et al.* (1988), found that after intramuscular injection in rats of PHB and PHB-PHV mild inflammation was detected, but this was associated to the injection vehicle or the trauma caused by the penetration of the needle rather than with the polymers or monomers. They also

reported that the polymers caused no inhibition in the growth of CHO-K1 cells in culture (these cells are a useful model of mammalian cells), but the cells were proven to be sensitive to the presence of monomers above concentrations of 10 $mg.ml^{-1}$, suggesting that high concentrations of monomer may be expected to have a deleterious effect on the metabolism of the surrounding tissue. However, it is not likely that such concentrations would be present *in vivo*, because degradation of the polymer is slow and free monomer would be expected to be rapidly cleared from the site of polymer implantation.

Gilding (1981) showed that the thermal processing caused PHB degradation. However, its copolymers with poly(3-hydroxy valerate) (PHV) have good melt stability and can therefore be easily processed to matrices for controlled drug delivery (Holland *et al.*, 1986).

The release of hydroxyethyltheophylline from PHB matrices has been reported to be diffusion controlled with high drug loadings, but both diffusion and degradation controlled with low loadings (Korsatko *et al.*, 1983 a,b). Drug release from PHB-PHV compressed matrices has been shown to depend on the MW of the drug, the copolymer composition, the drug loading, and the porosity of the matrix (Gould *et al.*, 1987).

1.2.3.1.3 Polydioxanones and polyoxylates

Polydioxanone and polyoxylates have been primarily synthesized for use as bioabsorbable surgical sutures (Holland *et al.*, 1986) The commercial suture Maxon is a copolymer of 1,3 dioxane-2-one (32.5%) and glycolide, and has been reported to have better handling properties than the equivalent polyglycolide suture Dexon (Katz *et al.*, 1985).

Copolymers of polydioxanones and polyoxylates with the structurally similar poly(lactide) and poly(glycolide) have been suggested for the preparation of controlled drug delivery systems (Shalaby and Jamiolkowski, 1978; Guerrero *et al.*, 1980). However, further research is needed to evaluate in detail their biodegradation and biocompatibility (Holland *et al.*, 1986).

1.2.3.1.4 Polyamides

Nylons are not considered biodegradable materials even though some of them are hydrophillic and hydrolysable, undergoing slow biodegradation. Moiseev (1979) and Gumargalieve (1980) demonstrated hydrolytic and enzyme catalyzed surface degradation of nylon 6.6 implants both *in vitro* and *in vivo*. The implants lost 80% of their initial tensile strength during three years implantation in dogs.

Poly(amino acids) have been shown to degrade enzymatically both *in vitro* and *in vivo* (Williams, 1982). The hydrolytic instability of the amide bond has been used in the

preparation of polymers designed to give controlled biodegradation via the introduction of segments susceptible to the affects of specific enzymes (Kopecek, 1981).

Copolymers of glutamic acid and p-ethyl-l-glutamate have been used as biodegradable membranes in the release of the narcotic antagonist naltrexone and as monolithic devices for the delivery of contraceptive steroids (Sidman *et al.*, 1979 and 1980). The same copolymers have been used to prepare hydrogel membranes, permeable to proteins with a mw range of 12 x 10^3 to 69 x 10^3 (Sidman *et al.*, 1983). Poly(amino acids) have also been utilized as chemical carriers of active agents (paragraph 1.2.2).

1.2.3.1.5 Poly(cyano acrylates)

Alkyl cyanoacrylates can undergo a very rapid polymerization and adhere firmly to moist tissue. They have evoked considerable interest as surgical adhesives (Leonard *et al.*,1967).

Poly(cyano acrylates) have been shown to undergo hydrolytic degradation by a reverse knoevenagel reaction (Leonard *et al.*, 1966, Vazin and Florence,1980). The rate of degradation depends on the length of monomer alkyl chain, and on MW and MWD of the polymer. It is also affected by the size and specific surface area of the polymer and by the pH of the dissolution medium (Vezin and Florence,1980). Poly(methyl cyanoacrylate) is histotoxic due to the rapid degradation and accumulation of degradation products.

Poly(butyl cyanoacrylate) is better tolerated (Lechman *et al.*, 1966; Mungiu *et al.*, 1979). The toxicity of poly(alkyl cyanoacrylate) nanoparticles, free and doxorubicin loaded, has been investigated. It was demonstrated that the nanoparticles induced cellular damage only at concentration of 1% or greater in the culture medium, and therefore can be safely utilized as drug carriers (Kante *et al.*, 1982; Couvreur *et al.*, 1982).

Biodegradable microcapsules (Florence *et al.*, 1976; Florence *et al.*, 1979) and magnetic particles for drug targeting (Ibrahim *et al.*, 1983) have also been prepared using poly(alkyl cyanoacrylates).

1.2.3.1.6 Polyanhydrides

Polyanhydrides undergo a controlled heterogeneous degradation which can be used to regulate the rate of drug release from polyanhydride formulations (Chasin *et al.*, 1990).

Polyanhydrides of high MW can be prepared by melt polycondensation. The factors affecting the MW are monomer purity, time, temperature of polymerization and the type of catalyst. Significantly higher molecular weights were achieved using shorter polymerization periods with catalysts, such as cadmium acetate, earth metal oxides and diethyl zinc-water (Domb and Langer,1987). Polyanhydrides homopolymers such as poly(carboxy phenoxy acetic acid) (PCPA) and copolymers, such as the copolymer of bis

carboxyphenoxypropane and sebacic acid, P(CPP-SA) have been synthesized.

The degradation of polyanhydrides involves hydrolysis of the anhydride linkage, which proceeds in an essentially constant rate. The degradation rate depends on the length of the aliphatic chain in the polymer backbone decreasing with an increase in chain lengthening. The relative ratio of the two monomers has a marked effect on the degradation rate of polyanhydride copolymers. By altering the carboxyphenoxypropane - sebasic acid ratio in the P (CPP-SA) copolymer, nearly any degradation time between 1 day and 3 years can be achieved (Leong *et al.*, 1985).

Release studies for anticancer agents (Chasin *et al.*, 1988; Grossman *et al.*, 1988), steroids (Leong *et al.*, 1986a) and proteins (Mathiowitz *et al.*, 1985; Mathiowitz and Langer,1987;) incorporated in polyanhydride matrices, or microcapsules, showed that these polymers are capable of delivering a wide range of drugs for prolonged periods of time. Biocompatibility tests for polyanhydrides gave satisfactory results (Leong *et al.*, 1986b; Brem *et al.*, 1988a,b). P (CPP-SA) loaded with the cancer chemotherapeutic agent carmustine is currently studied in man, for the local treatment of brain cancer. The safety of this material has been demonstrated (Chasin *et al.*, 1990).

1.2.3.1.7 Poly(ortho esters)

Poly(ortho esters) have been developed for the preparation of delivery systems where drug release would be predominantly controlled by a surface degradation process (Heller *et al.*, 1990).

Poly(ortho esters) useful in the fabrication of controlled release devices have been synthesized by the addition of polyols to diketene acetals (Heller *et al.*, 1980). The reaction proceeds spontaneously but when catalyzed by small amount of acids, high MW polymers are formed virtually instantaneously. The MW can be regulated by appropriate skewing of the stoichiometry of the monomers' mixture. The mechanical properties of poly(ortho esters) can be varied within wide limits by careful selection of the diol or the mixture of diols (Heller *et al.*, ~~1983~~ 1983a; Heller *et al.*, 1989).

The initial degradation products of these poly(ortho esters) are the diol and the pentaerythritol ester. The pentaerythritol ester hydrolyzes at a slower rate to pentaerythritol and the corresponding aliphatic acid. The rate of degradation decreases with an increase in the polymer MW (Sparer *et al.*, 1984).

Because orthoester linkages are acid sensitive, but stable in basic media, the degradation can be controlled by incorporating acidic or basic excipients in the formulation (Heller,1985). Acidic excipients have been used to prepare

surface degrading devices having a relatively short duration of drug release (Sparer *et al.*, 1984).

Another method of accelerating the degradation, without employing excipients, is the introduction of pendant carboxylic acid groups in the polymer backbone, which upon ionization in the water catalyze the hydrolysis of the polymer (Heller *et al.*, 1984).

The degradation rate and consequently the rate of drug release can be decreased by incorporating basic excipients into the matrix. Thus the release of levonorgestrel from rods containing 71% mol magnesium hydroxide implanted subcutaneously in rabbits occurred concomitantly with the degradation of the polymer for at least 20 weeks (Heller *et al.*, 1985). A plausible mechanism for the degradation of devices containing magnesium hydroxide is that the base stabilizes the interior of the device and degradation then only occurs in the surface layers where the base has been eluted or neutralized (Heller,1986).

1.2.3.1.8 Polyphosphazenes

Polyphosphazenes are a new class of polymers which can be either biodegradable or non-biodegradable by changing the side groups attached to an unconventional macromolecular backbone (Allcock,1990). A wide range of polyphosphazene molecular structures can be obtained by either substitution reactions involving the macromolecular intermediate poly(dichlorophosphazene) or polymerization of a cyclic

trimer whose chloro side groups have been previously replaced by organic groups (Allcock *et al.*, 1966; Allcock *et al.*, 1978; Allcock and Moore,1975). The properties of the polymer, such as crystallinity and hydrophilicity, depend on the type and disposition of different groups (Allcock,1990).

Water-insoluble biodegradable polyphosphazenes have been used for the preparation of matrix controlled drug release systems. The sustained release of progesterone and bovine serum albumin from matrices based on imidazole-methylphenoxy polyphosphazene copolymers has been demonstrated. A lag period of 80 hours, followed by a period of almost constant release for 900 hours, was observed with progesterone discs implanted subcutaneously in rats. The release of bovine serum albumin exhibited an initial burst of 25% which could be eliminated by coating the matrices with polymer (Laurencin *et al.*, 1987). Insoluble biodegradable polyphosphazenes have also been used as chemical carriers for the chemically controlled release of steroids (Allcock and Fuller,1980), antibacterial agents (Allcock and Austin,1981), local anaesthetics (Allcock *et al.*, 1982_a) and polypeptides (Allcock *et al.*, 1982_b).

Water-soluble macromolecular drugs could be more effective in some forms of therapy than their small molecular counterparts because of their restricted ability to escape through biological membranes. Furthermore, targeting groups can also be linked to the macromolecule to increase

the effectiveness of the drug (Allcock,1990). The properties of macromelecular drugs have been exploited to reduce the side effects of the antitumour agent $(NH_3)_2\ PtCl_2$. Kidney damage, caused by the readily excreted drug, can be reduced by its reaction with poly(bis-methylamino-phosphazene), in which a non-excretable co-ordination complex is formed (Allen *et al.*, 1977).

1.3 Poly(lactide-co-glycolide) Polymers

1.3.1 Introduction

Glycolic acid and lactic acid are the common names of the first two α-hydroxycarboxylic acids, α-hydroxyacetic and α-hydroxypropionic acid:

Glycolic Acid Lactic Acid

Lactic acid contains an asymmetric carbon atom and therefore has two optical isomers:

L(+) D(-)

When condensed the direction of rotation of sodium D line is reversed, so that L (+) lactic acid gives L(-) lactide and L(-) polylactic acid and D(-) lactic acid give D(+) lactide and D(+) polylactic acid (Wise *et al.*, 1979_a).

Six membered cyclic dimers of lactic or glycolic acid- lactide (LE) and glycolide (GE) respectively (Fig. 2) - can be synthesized by removing the free water and much of the bound water from an aqueous solution of the appropriate acid by vacuum distillation. The cyclization occurs in the vapour phase (Wise *et al.*, 1979_a).

They are white, crystalline, very hygroscopic materials which are readily hydrolysed in the presence of moisture. Lactide contains two asymmetric carbon atoms and exists as four different diastereomeric compounds, the L,L and D,D antipodes (L(-) and D(+) lactides respectively), the D,L diastereomer or meso-lactide, and the D,D and L,L racemic combination of L(-) and D(+) lactides (racemic lactide), depending on the L and D configuration of the lactic moieties forming the cyclic molecules (Fig 3). Racemic lactide consists largely of a mixture of D and L lactide, not the mesoform. The melting point of this mixture is higher than that of the individual components (Chabot *et al.*, 1983).

isomer:	l-lactide	D-lactide	D,L-lactide	Meso-lactide
Melting: Point. (^{o}C)	95-36	95-36	124-126	41-42

Glycolide (melting point 82^{o}C) exists in two isomeric configurations resulting in two crystal forms designated α and β (Fig. 4). The α crystal is thermodynamically preferred if crystallization occurs above 42°C, the β crystal form below that temperature.

The α form has been found to be more stable hydrolytically and is therefore preferred for use in preparing high MW polymers. It is slowly but unpredictably converted to the β isomer on standing at ambient temperature (Frazza and Schmitt, 1971).

1.3.2 Synthesis of poly(lactide-co-glycolide) polymers

Low molecular weight polymers can be prepared by the direct polyesterification of lactic and/or glycolic acids. Condensation of α-hydroxycarboxylic acids can be effected by the removal of water by boiling it from the reaction mixture, or by azeotropic distillation with an aromatic hydrocarbon solvent (Fig. 5) (Filachione and Fischer,1944). At reaction temperatures below 120°C an acid, such as toluene sulphonic acid or sulphuric acid, beneficially increases the reaction rate, but above this temperature the rate-limiting step is generally water removal, so that little benefit is gained by employing a catalyst. An upper limit for number overage molecular weight of approximately 10000 exists for polymers produced using the step growth condensation reaction (Fig. 5) (Wise *et al.*, 1979_a).

In order to prepare higher MW polymers it is necessary to proceed by ring opening of the cyclic diesters, lactide and glycolide. This ring opening polymerization has been shown to proceed through pair addition of lactic or glycolic acid units yielding polydimers (Fig. 6). As many of the catalysts for the ring opening polymerization do not alter the lactide configuration, this pair addition mechanism of

chain growth provides a means to synthesize polymers with various configurational structures, or tacticity, from suitable mixtures of lactide diastereoisomers. The resulting stereocopolymers have been shown to contain the monomeric units in the same proportion as that of the monomer mixture, which implies that the reactivities of the optically active and racemic monomers are the same (Chabot *et al.*, 1983). Because glycolide has been found to be more reactive than lactide (Gilding and Reed,1979) it is probable that copolymers containing blocks of glycolic acid repeating units will be produced rather than copolymers of a random structure.

Ring opening polymerization can be effected in solution or in a melt. Solution polymerization proceeds in a suitable organic solvent such as chloroform, toluene or dioxane. As low temperatures are employed (25 to 80^{o}C) long reaction periods (12 hours to a few days) are necessary to obtain high molecular weights and satisfactory conversion. Solution polymerization involves relatively mild conditions, allowing better control of the reaction, and it was therefore, preferred to melt polymerization when studies on the mechanism, or kinetics, of polymerization were carried out. A co-ordinate polymerization mechanism has been proposed for the solution polymerization of lactide (Dittrich and Schultz,1971).

For biomedical application poly(lactide-co-glycolide) polymers have been prepared by melt polymerization, which is more rapid and convenient than solution polymerization.

Monomers of high purity and low acidity are required in order for high MW polymers to be obtained (Lowe,1954). The exclusion of moisture is also essential because it may cause termination of the chain growth reactions, or hydrolysis of the monomers to acidic products. Schindler *et al.* (1977) reported that high MW polymers were obtained only with the use of silanized glass vessels.

Jacobson (1970) argued that the amount and type of catalyst used would determine the particular temperature and time required to produce the polymer. He suggested that, as a rule, the lower the amount of catalyst, the longer the time required to produce polymer of a given MW and conversely the higher the catalyst concentration the shorter the time. Melt polymerization is usually conducted over a period of 2-6 hours at about 160-220^{o}C. With crystalline polymers, such as poly(glycolide), it has been reported as preferable that the polymerization is initiated at a temperature below the melting point of the polymer, and when solidification of the polymer produced commences the temperature is raised above the melting point to prevent solidification and to complete polymerization (Lowe,1954; Chujo *et al.*, 1967).

Lactones can be polymerized by both cationic or anionic mechanisms (Cherdron, 1962), therefore, a variety of catalysts have been employed to polymerize lactide and/or glycolide.

For intermediate molecular weights (10000 - 40000) protic acid catalyzed polymerizations are convenient and

effective. If the concentration of reactive impurities is less than the catalyst concentration, then the mw is determined by the catalyst concentration (Wise *et al.*, 1979a). Thus, lactide and glycolide were bulk polymerized at 130°C with p-toluenesulphonic acid as a catalyst for 7-10 days and the resulting material was a solid golden mass (Kitchell and Wise,1985). Glycolide was polymerized using sulphuric acid or phosphoric acid and a brittle and highly coloured polymer resulted (Chujo *et al.*, 1967).

Tertiary amines, such as triethylamine, trimethyl amine and diethyl-n-butylamine, have been used for the anionic solution polymerization of glycolide (Klootwijk,1966; Braun and Kohl,1976).

Oxides of zinc, magnesium, cadmium, lead and antimony have been reported as suitable catalysts for the melt polymerization of lactide and/or lactide (Kulkarni *et al.*, 1966; Jacobson,1970). Powdered zinc has also been used successfully in the preparation of poly(lactide) stereocopolymers (Chabot *et al.*, 1983).

Polymers with high molecular weights can be synthesized using Lewis acids, such as zinc chloride, aluminium chloride, tin tetrachloride, and antimony trifluoride, or organometallic compounds and salts, such as dialkyl zinc, trialkyl aluminium, tetralkyl tin complexes, and stannous octoate, as catalysts (Tsuruta *et al.*, 1964; Chujo *et al.*, 1967; Gilding and Reed,1979). It is presumed that the polymerization mechanism with organometallic catalysts

involves nucleophilic attack of a carbonyl on one of the lactide or glycolide carbonyls. The effect of catalyst concentration on polymer molecular weight is not as clear in the case of organometallic catalysts as it is in the case of acid catalysts (Wise *et al.*, 1979a).

1.3.3 Poly(lactide-co-glycolide) Properties

One important advantage of poly(lactide-co-glycolide) polymers - and the one that characterizes this family of polymers - is the variability in polymer properties. A broad spectrum of performance characteristics can be obtained by careful manipulation of three key variables: composition (lactide:glycolide ratio), monomer stereochemistry, and molecular weight

1.3.3.1 Physical Properties of Poly(lactide-co-glycolide)

1.3.3.1.1 Solubility

Solubility of the polymers in common organic solvents is an important factor with regard to fabrication of drug delivery dosage forms. Poly(dl-lactide) and poly(dl-lactide-co-glycolide) with less than 50 mol % in glycolic acid units content are soluble in acetone, ethylacetate, tetrahydrofuran, dioxan, benzene and halogenated hydrocarbons (e.g. chloroform, methylene chloride). Poly(l-lactide) is soluble only in chlorinated solvents at ambient temperature, but is soluble in benzene at an elevated temperature (Kulkarni *et al.*, 1971; Schindler and

Harper,1979; Deasy *et al.*, 1989). Poly(glycolide) and glycolide-rich copolymers are quite insoluble materials. Exotic solvents such as hexafluorisopropanol (HFIP), are often used in analytical procedures as solvents for these polymers (Gilding and Reed,1979).

Recently, the solubility parameters (δ) of certain biodegradable polymers were determined (Siemann, 1985). The δ values for poly(l-lactide), poly(dl-lactide) and a 58:42 (LE:GE % mol) polymer were, surprisingly, very similar [ranging from 16.4 to 16.8 X $10^3(JM^{-3})^{0.5}$] and reflected the hydrophobic character of these polymers. The δ values for tetrahydrofuran and chloroform, which are good solvents for these polymers, were of the same magnitude in accordance with the solubility parameter concept [δ for chloroform 13.0 X 10^3 and for tetrahydrofuran 18.6 X $10^3(JM^{-3})^{0.5}$].

1.3.3.1.2 Crystallinity

The crystallinity, the glass transition temperature (Tg) and the melting point of poly(lactide-co-glycolide) polymers depend on their composition and the enantiomeric composition of lactide units in the polymer (Gilding and Reed,1979; Vert *et al.*, 1981).

Typical crystallinities for poly(glycolide) sutures are 46-52% whilst for poly(l-lactide) the crystallinity is 37%. Poly(dl-lactide) and poly(dl-lactide-co-glycolide) with 0-70 mol % glycolic acid units content are amorphous.

Poly(l-lactide-co-glycolide) having 25-70 Mol% glycolic acid units is also amorphous (Gilding and Reed,1979). The melting points of poly(l-lactide) and poly(glycolide) are in the range 170-180^{o}C and 220-230^{o}C respectively (Lewis,1990). Although poly(dl-lactide) is amorphous, it undergoes a solid-melt transition in the region of 130-135^{o}C (Holland *et al.*, 1986). Glass transition temperatures range from 36^{o}C for poly(glycolide) to 65^{o}C for poly(l-lactide) (Lewis,1990).

1.3.3.1.3 Thermal Behaviour

Poly(lactide-co-glycolide) polymers are thermoplastic materials, stable enough to be heat processed, providing moisture is absent, for the fabrication of prosthetic or drug delivery implants and surgical sutures. After prolonged heating above 200^{o}C, under nitrogen or vacuum, the polymers degrade to lactide and/or glycolide (Gilding and Reed,1979). At lower temperatures thermal degradation is a time/temperature function and is considerably accelerated by impurities, residual monomers and humidity (Boehringer Ingelheim, personal communication,1989).

1.3.3.1.4 Water Uptake

Composition and monomer stereochemistry affect the water uptake and hydration rate of poly(lactide-co-glycolide) polymers.

Gilding and Reed (1979), working with poly(l-lactide-co-glycolide) films, showed that equilibrium water content (% water absorbed until constant weight, normally after 3-4 days of immersion in phosphate buffer, pH = 7.4) increases with the increase in glycolide content and reaches a maximum of ~30% at 70 mol% glycolide, decreasing thereafter as the crystallinity of the polymers increases. However, Dunn *et al.* (1988), working with poly(dl-lactide-co-glycolide) films reported that the polymers continued to absorb water steadily, even after 25 days immersion in milli-Q water, to reach much higher water contents than those reported by Gilding and Reed (1979). Pitt and Gu (1987) reported very low water uptake values of 0.84 and 0.57 % for a 70:30 (LE:GE % mole) polymer and poly(l-lactide) respectively, without any reference on the method of measurement.

1.3.3.2 Molecular Weight of Poly(lactide-co-glycolide)

The most important feature distinguishing polymers from low molecular weight species is the existence of a distribution of chain lengths. Because of the existence of this distribution in any finite sample of polymer, the experimental measurement of molecular weight can give only an average value (Billmeyer,1984).

Some methods of mw measurement are based on counting the number of molecules in a known mass of material (e.g., methods based on colligative properties of polymer

solution), leading to the number-average molecular weight M_n:

$$M_n = \frac{\sum_{i=1}^{\infty} M_i N_i}{\sum_{i=1}^{\infty} N_i} \qquad \text{Equation 2}$$

where N_i is the number of molecules in the sample having molecular weight M_i

In other methods the parameter measured is proportional to the mass of the molecule (e.g., methods based on light scattering from solutions of polymers). With these methods the weight-average molecular weight M_w is determined:

$$M_w = \frac{\sum_{i=1}^{\infty} N_i M_i^2}{\sum_{i=1}^{\infty} N_i M_i} \qquad \text{Equation 3}$$

From the above equations it is obvious that M_w is always bigger than M_n. The ratio M_w/M_n defines the polydispersity of a polymer and is a measure of the breadth of the molecular weight distribution curve. The molecular weight distribution (MWD) of a polymer sample can be determined by size exclusion chromatography (Billmeyer,1984).

The viscosity of a polymer solution is a measure of the size or extension in space of polymer molecules and is empirically related to mw for linear polymers, through the Mark-Houwink equation:

$$[n] = K(MW)^{\alpha}$$ Equation 4

In equation (4) [n] is the intrinsic viscosity of the polymer and K, α constants characteristic for a particular polymer-solvent system at a given temperature. For many systems α lies between 0.6 and 0.8. Typical values of K range between 0.5 X 10^{-4} and 5 X 10^{-4} (Billmeyer,1984).

The intrinsic viscosity (or limiting viscosity number) is the reduced viscosity or the inherent viscosity extrapolated to infinite dilution:

$$[n] = \lim n_{red} = \lim \frac{n_{sp}}{C}$$ Equation 5

$$[n] = \lim n_{inh} = \lim \frac{\ln n_{rel}}{C}$$ Equation 6

It can thus be determined by extrapolating to zero concentration plots of reduced or inherent viscosity versus concentration. Alternatively it can be calculated by the Solomon-Ciuta (1962) approximate equation:

$$[n] = \frac{1}{C}\left[2\left(n_{sp} - \ln n_{rel}\right)\right]^{1/2}$$ Equation 7

Intrinsic viscosity measurement leads to the viscosity-average Molecular weight, Mu:

$$M_u = \frac{\sum_{i=1}^{\infty} N_i M_i^{1+\alpha}}{\sum_{i=1}^{\infty} N_i M_i} \qquad \text{Equation 8}$$

For many polymers Mu is 10-20% below M_w. If the MWD of the samples is known in sufficient detail to calculate from a molecular weight average that has been measured, the constants in the equation:

$$[n] = K.M_U^{\alpha} \qquad \text{Equation 9}$$

can be calculated. A less precise relation:

$$[n] = K.M_W^{\alpha} \qquad \text{Equation 10}$$

is sometimes used to relate weight average molecular weight directly to intrinsic viscosity for a limited series of samples (Billmeyer,1984).

The molecular characterization of polymers using the Mark-Houwink equation is the most frequently applied method because of the simplicity, speed and accuracy of viscometry (Quackenbos,1980). Schindler and Harper (1979), Rak *et al*.

(1985) and Deasy *et al.* (1989) determined Mark-Houwink constants for poly(lactide). Wise *et al.* (1979a) and Pitt and Gu (1987) reported Mark-Houwink constants for poly(lactide-co-glycolide) polymers. These are tabulated in Table 1.

The polydispersity of poly(lactide-co-glycolide) polymers is usually around 2 indicating a fairly uniform polymer chain length (Gresser *et al.*, 1989; Rak *et al.*, 1985).

1.3.3.3 Mechanical Properties

The strength of poly(lactide-co-glycolide) depends on composition, monomer stereochemistry, mw and processing. The strength of crystalline poly(l-lactide) and poly(glycolide) is considerably higher than that of the less crystalline poly(dl-lactide) and poly(lactide-co-glycolide) (Gilding and Reed,1979; Vert *et al.*, 1981). Rak *et al.* (1985) found a linear relationship between mw and Young's Modulus of elasticity (E) and the energy required to break poly(dl-lactide) films. Also, the tensile strengths (T) of the films increased with an increase in polymer mw, ranging from 2.6 to 6.9 MPa.

Vert *et al.* (1981) showed that the strength (E,T) of PLA implants decreases with the increase in D units in the polymer. Tensile strength ranged from 64 MPa for poly(l-lactide) to 42 MPa for poly(dl-lactide). Poly(l-lactide) matrix reinforced with poly(glycolide) fibres has the necessary strength to be used as a completely absorbable

composite material for the osteosynthesis of human fractures (Vert *et al.*, 1984).

1.3.3.4 Biodegradation of Poly(lactide-co-glycolide)

Poly(lactide-co-glycolide) polymers are hydrolytically biodegraded into lactic and glycolic acid and eliminated from the body through the krebs cycle, primarily as carbon dioxide and in urine. There appears to be no differences in the rate of poly(lactide-co-glycolide) degradation in different body tissues (Kulkarni *et al.*, 1966; Brady *et al.*, 1973; Miller *et al.*, 1977).

The mechanism of poly(lactide) biodegradation has been proposed to be a two stage process (Pitt *et al.*, ~~1981~~ 1981b; Pitt and Gu,1987). During the first stage random hydrolytic cleavage of ester bonds occurs, which is believed to be autocatalyzed by the carboxylic acid groups generated. The chain scission process appears to follow first order kinetics. There is no enzymatic involvement at this stage as indicated by observation of the same degradation kinetics *in vitro*. The second stage is characterized by the onset of mass loss from the polymer matrix and an increase in the rate of chain scission. The mass loss begins when the polymer has been degraded to a molecular weight level below that required for coherence and chain fragments small enough to dissolve in the degradation liquid and diffuse out from the matrix have been produced (Kronenthal,1975).

So far, enzymatic involvement in the biodegradation of poly(lactide-co-glycolide) polymers has not been ascertained, although it has been shown that some enzymes accelerate the degradation *in vitro* of poly(glycolide) sutures and poly(lactide) powders (Williams, 1981; Williams and Mort, 1977). Differences between the *in vitro* and the *in vivo* degradation profiles have been also reported (Williams,1982). However, the aforementioned cannot be considered adequate proof of the role of enzymes in the biodegradation of poly(lactide-co-glycolide) since enzymes are not the only species in the physiological environment. Thus, Williams (1982) reported that lipids affect significantly the degradation *in vitro* of poly(glycolide) sutures. Also, tissue encapsulation of the polymer matrix *in vivo* may inhibit the removal of degradation products from the matrix resulting in poor correlation between *in vitro* and *in vivo* degradation data. Holland *et al.* (1986), suggested that for polymers in the glassy state little enzymatic involvement could be expected in the early stages of degradation. This may become more marked in the later stages, however, as erosion and physical fragmentation of the polymer occurs.

An increase in the molecular weight caused an increase in the biodegradation time of poly(dl-lactide) polymers (Chawla and Chang,1986; Ogawa *et al.*, 1988$_c$), whilst an increase in glycolide content initially increased and then decreased the biodegradation rate of poly(lactide-co-glycolide) polymers (Miller *et al.*, 1977; Reed and

Gilding,1981). The turning point in poly(lactide-co-glycolide) biodegradability appears to be a matter of controversy. Miller *et al.*,(1977) found that the 50:50 (LE:GE %mol) composition had the lowest biodegradation half life (approx. 1 week), whilst Reed and Gilding (1981) reported that the most hydrated composition, i.e. the 30:70 (LE:GE % mol) was also the fastest degraded *in vitro*. The 30:70 copolymer began to fragment at 12 days, and underwent 100% mass loss within 4 weeks *in vitro*. By changing the composition polymers with a degradation time from a few weeks to more than one year can be obtained (Lewis, 1990).

Pitt and Gu (1987) reported that the degradation rate *in vitro* of a 70:30 (l-LE:GE %mol) was 17 times greater than that of poly(l-lactide). This was attributed to the greater susceptibility of glycolate ester to hydrolysis, coupled with some plasticization of the copolymer by the absorbed water. However, Fredericks *et al.* (1984) reported that there was no preferential attack on either the lactide or glycolide units of a random 8:92 (l-LE:GE %mol) polymer despite the difference in their hydrophilicity.

For the crystalline poly(lactide-co-glycolide) polymers used as surgical sutures (Dexon, Vicryl) an almost complete loss of strength is observed before any mass loss takes place (Craig *et al.*, 1975; Chu,1985). Because the amorphous regions of the polymer hydrolysed first, it becomes apparent that the strength of the suture relies on molecules in these regions. These may be tie molecules connecting the crystallites (Fredericks *et al.*, 1984).

Vert *et al.* (1981,1984) showed that increasing the content in D units in poly(lactide) stereo copolymers increased the biodegradation rate. Poly(l-lactide) appears to be the more biostable member in the poly(lactide-co-glycolide) family.

Beck *et al.* (1983_a) reported that the biodegradation rate of poly(lactide-co-glycolide) microspheres containing norethisterone increased with an increase in the size of the injected microspheres, which was attributed to the increased surface area of the smaller microspheres.

Processing and annealing could affect the biodegradation rate of poly(lactide-co-glycolide) polymers (Vert *et al.*, 1981). Gilding and Reed (1979) showed that γ radiation causes degradation of poly(lactide-co-glycolide). The formation of low molecular weight compounds during the sterilization of the ready for implantation end-products by means of γ radiation may significantly accelerate the biodegradation rate of poly(lactide-co-glycolide) polymers (Vert *et al.*, 1984).

Dunn *et al.* (1988) argued that the microstructure of poly(lactide-co-glycolide) polymers can affect their degradation rate, and differences in the solubility and degradation of two different samples of a copolymer, with the same monomer ratio were attributed to differences in the sequence of monomer units in the copolymer chains.

1.3.3.5 Biocompatibility and Tissue Reactions

The biocompatibility and non toxicity of poly(lactide-co-glycolide) polymers was first demonstrated in the process of developing biodegradable sutures. Sutures from poly(glycolide) and 10:90 (l-LE:GE %mol) polymer have been found to be non toxic, inert, non antigenic and non pyrogenic (Merrit *et al.*, 1974).

In experiments with animals, involving poly(lactide-co-glycolide) implants in bone and soft tissues, none or only mild inflammatory response, which diminishes with time, has been found in most studies (Kulkarni *et al.*, 1966; Brady *et al.*, 1973; Getter *et al.*, 1972; Cutright *et al.*, 1974; Vert *et al.*, 1984). The lack of inflammatory response indicates inertness and tissue receptivity. No implant migration or rejection, nor allergic responses have been reported (Wise *et al.*, 1979a).

However, poor biocompatibility of poly(lactide) implants has also been reported. Thus, poly(dl-lactide) microparticles (1-10μ) were found to cause inflammation after intra-articular injection into the knee joints of rabbits (Ratcliffe *et al.*, 1984). The same microparticles were found to stimulate the release of lysosomal enzyme from cultured macrophages, which may explain their inflammatory action *in vivo*. By contrast a none inflammatory response was observed when the microparticles were compressed into small tablets and implanted subcutaneously in rats (Smith and Hunneyball, 1986).

The tolerance of tissues to implanted articles is not only determined by the pure material properties. The site, surface characteristics and shape of the implant may also have an influence on tissue response (Graham and Wood,1984).

The reactions of soft tissues to poly(lactide-co-glycolide) implants involve accumulation of foreign body giant cells and marked fibroblastic activity. The implants are gradually surrounded and invaded by tissue fibres until finally absorbed and replaced by connective tissue (Kulkarni *et al.*, 1966; Brady *et al.*, 1973).

Similar responses have been observed when poly(lactide-co-glycolide) particles were implanted intra-osteally. Upon implantation mild foreign body reaction is elicited with an accumulation of histocytes and mast cells in close vicinity to the implant which is gradually encapsulated by bone and connective tissue. Polymer degradation is accompanied by a fibrous invasion of the cracks which develop. This contains giant cells and mononucleated cells. The implant is finally replaced by bone or marrow tissue (Vert *et al.*, 1984; Tunc *et al.*, 1985).

There exist few reports in the literature concerning the application of poly(lactide-co-glycolide) implants in human subjects. Little polymer particles were used for the fixation of fractures of the skull and jaw. According to preliminary clinical results all fractures healed in a

normal way. No acute or chronic tissue reactions were observed (Vert *et al.*, 1984).

Brekke *et al.* (1983) applied poly(lactide) mesh as a surgical dressing in the healing of dental extraction wounds. The poly(lactide) dressing was well tolerated by the tissue and showed no adverse effects on normal healing. The incidence of localized osteitis following mandibular third molar extractions was significantly reduced by the application of the poly(lactide) dressings. Rokkanen *et al.* (1985) found no difference in the outcome between two groups of patients with displaced fractures of the ankle treated with conventional metallic implants and poly(lactide-co-glycolide) implants, respectively.

1.3.3.6 Fabrication Techniques

Poly(lactide-co-glycolide) polymers are generally low melting thermoplastic materials with good solubility in common organic solvents, glycolide-rich polymers being the exceptions. These properties allow considerable flexibility in the fabrication of drug delivery systems. Three types of delivery systems based on poly(lactide-co-glycolide) polymers have been investigated : Microparticles, implants and fibres.

Microspheres and microcapsules of poly(lactide-co-glycolide) polymers can be prepared using standard microencapsulation techniques (Maulding,1987). A solvent evaporation procedure particularly useful for entrapment of

water insoluble drugs has been developed (Beck *et al.*, 1979; Tice and Lewis,1983). The reproducibility and scale-up of this procedure was demonstrated with a contraceptive formulation having a lifetime of 90 days (Lewis *et al.*, 1988). Organic phase separation techniques are suitable for incorporation of water soluble peptides and macromolecules into microspheres, on either a relatively large or a small batch size (Fong,1979; Kent *et al.*, 1984). Processes based on spray-drying or fluidized bed coating have also been developed (Wise *et al.*, 1976; Nuwayser and Deroo, 1987; Bodmeier and Chen,1988).

Standard methods of processing thermoplastic polymers can be employed to fabricate implantable articles from poly(lactide-co-glycolide) polymers. In these methods high temperature and pressure are usually involved, and care should be therefore exercised to keep moisture levels in the materials and humidity in the working areas as low as possible to avoid polymer degradation. Considerations of importance when selecting fabrication methods are heat stability of polymer and active agent, the polymer softening temperature, and the size and shape of the end product (Billmeyer,1984).

Poly(lactide-co-glycolide) films can be prepared by casting a solution of the polymer in a volatile solvent containing the drug or by compression moulding of polymer and drug mixtures (Jackanicz *et al.*, 1973; Hutchinson,1982).

Implants in the form of beads have been prepared by transfer moulding of film pieces (Schwope *et al.*, 1975) and in the form of small cylinders by extrusion of film pieces or freeze dried powders (Schwope *et al.*, 1975; Gresser *et al.*, 1978; Hutchinson,1982; Kitchell and Wise 1985).

Reservoir poly(lactide-co-glycolide) implants in the form of coated pellets or capsules have also been studied (Boswell and Scribner,1973; Pitt *et al.*, 1979; Marcotte *et al.*, 1990). A technique for the preparation of porous capsules, suitable for controlled delivery of macromolecules, has been developed by Schindler (1987). Monolithic fibres can be prepared by melt extrusion of polymer and drug mixtures, and reservoir fibres have been prepared either by a melt spinning technique or by a wet phase inversion process (Dunn*et al.*, 1981; Eenink *et al.*, 1987). In the latter method the drug is incorporated in the hollow fibre, after the fibres are produced and offers the possibility of utilizing drugs which are unstable under spinning conditions (Eenink *et al.*, 1987).

1.3.3.7 Sterilization Techniques

Gases, such as ethylene oxide, and γ radiation can be utilized for sterilization of poly(lactide-co-glycolide) drug delivery systems. However, ethylene oxide has been found to cause softening or plasticising of some poly(lactide) compositions (Lewis,1990). Residual vapour is also a problem since it has been shown to be mutagenic (Kitchell and Wise,1985).

The recommended sterilization method for poly(lactide-co-glycolide) products is γ radiation (Kitchell and Wise,1985) even though Gilding and Reed (1979) showed that γ radiation caused dose dependent degradation of poly(glycolide) sutures, probably through an unzipping mechanism. Also, Tice *et al.* (1982) reported that γ radiation decreased the inherent viscosity and increased the biodegradation rate of poly(lactide-co-glycolide) copolymers. In most cases doses of γ radiation ranging from 2.5 to 3.0 μrad can be utilized without serious degradation of the polymer (Lewis,1990).

Filter sterilization of drug-polymer solutions and aseptic preparation procedures are the alternative when sterilization of the final dosage form is not possible. Aseptic processing can be particularly useful with microencapsulated products which almost always involve solutions of the polymer in organic solvents.

1.3.4 Drug Poly(lactide-co-glycolide) Delivery Systems

A wide range of drugs have been incorporated in poly(lactide-co-glycolide) polymers including, steroids, narcotic antagonists, antimalarial drugs, anticancer agents, antiinflammatory drugs, local anaesthetics, antibiotics and bioactive macromolecules (polypeptides, proteins, and synthetic nucleic acids).

A growing number of polypeptides and proteins have recently been produced by recombinant DNA processes. Although they are highly potent and specific in their physiological

functions, most of them are difficult to administer clinically. They are generally not therapeutically active by oral administration and they have an extremely short biological half life when administered parenterally, and daily multiple injections are required. This therapeutic regimen is highly risky to administer without close medical supervision and also often difficult for most patients to accept. The development of sustained release formulations could be a significant improvement in the administration of such drugs (Banga and Chien,1988). However, bioactive macromolecules are usually characterized by complex three-dimensional structures, critical for their bioactivity. These molecules can easily be inactivated by both physical and chemical mechanisms, such as fragmentation, deamination, covalent dimerization, oxidation, unfolding, aggregation, and adsorption, therefore their incorporation in sustained release formulations is still a problem.

1.3.4.1 Contraceptive Steroid Systems

The controlled delivery of contraceptive steroids was one of the first applications of poly(lactide-co-glycolide) polymers. Implants (films, beads, rods) and granular particles were fabricated with progesterone, levonorgestrel and norethisterone (Jackanicz *et al.*, 1973; Anderson *et al.*, 1976; Yolles,1975; Wise *et al.*, 1978$_a$). None of these early systems have had significant clinical success, probably due to the polymers and fabrication methods used to prepare them (Lewis,1990).

Nevertheless, these early studies demonstrated the feasibility of extended controlled delivery of steroids using poly(lactide-co-glycolide) polymers and revealed the factors controlling the rate of release from such matrix systems. Thus, the release rate was found to depend on polymer composition, drug loading, and polymer molecular weight (Wise *et al.*, 1980).

Beck and co workers developed steroid load poly(dl-lactide-co-glycolide) microspheres using a patented solvent-evaporation technique (Beck *et al.*, 1979; Tice and Lewis,1983). The mechanism of steroid release from such microspheres was a combination of initial leaching and diffusion followed by biodegradation of the matrix (Tice and Cowsar,1984). The rate and duration of release was affected by the polymer composition, drug loading, size distribution and quality of the microspheres (Lewis and Tice 1983).

Often, biphasic release patterns have been observed with microspheres (Beck *et al.*, 1983a,b). The early elevated drug levels in blood are probably due to leaching and diffusion of the drug form the surface of the particles. The blood levels show a decline and when substantial degradation of the matrix occurs a second elevated drug level in blood is observed (Beck *et al.*, 1983a).

In practice these two regions have been made to merge by careful adjustment of the polymer properties and characteristics of the microspheres. Thus, by using an

85:15 poly(dl-lactide-co-glycolide) polymer a more constant rate of norethisterone release over the desired lifetime of the formulation (90 days) was obtained (Beck and Tice,1983). This formulation has recently undergone successful phase I and phase II clinical trials (Lewis *et al.*, 1988).

Poly(l-lactide) hollow fibres were prepared using a dry-wet phase inversion spinning process and filled with a 25% weight dispersion of micronized levonorgestrel in castor oil. Preliminary release experiments in rabbits showed that constant levonorgestrel blood plasma levels could be obtained over a 210 days period (Eenink *et al.*, 1987).

1.3.4.2 Narcotic Antagonist Systems

The first disclosure of the use of a synthetic biodegradable polymer for the systemic delivery of therapeutic agents was probably that made by Yolles *et al.* (1970), who described the release of cyclazosine from poly(lactide) films. The release was characterized by a large initial burst which was eliminated by encasing the film in a drug-free poly(lactide) film, thus, in effect converting a monolithic system to a diffusional one (Woodland *et al.*, 1973).

The release of the narcotic antagonists cyclazosine, naloxone, and naltrexone from poly(l-lactide) composites in particulate form has been investigated (Yolles, 1975). For cyclazosine and naltrexone *in vitro* release rates were

found to be faster than the *in vivo* release rates, whereas for naloxone they were similar. Particles with 100, 200 and 350μ average size released the drug at similar rates, but particles of 600μ released drug at considerably lower rate (Yolles,1975).

The release of naltrexone from spheres and rods has also been investigated (Schwope *et al.*, 1975). Naltrexone was found to dissolve readily in poly(dl-lactide) and in some poly(l-lactide) copolymers so that matrix systems with very high drug content (e.g. 80% by weight) could be prepared. The drug release *in vitro* was affected by drug content, copolymer composition, solubility of the drug in water, and geometry of the delivery system. Coating the beads with pure polymer also reduced the rate of naltrexone release (Schwope *et al.*, 1975). A good correlation between *in vitro* and *in vivo* (mice and monkeys) release data was obtained with these formulations (Wise *et al.*, 1979$_a$).

Naltrexone was also encapsulated in poly(lactide-co-caprolactone) (10:90) copolymers using a microfluidized bed coating process (Nuwayser *et al.*, 1988). Uncoated poly(l-lactide-co-glycolide) microcapsules released 80% of their drug content in phosphate buffer within 2 days. Coating the microcapsules with additional polymer slowed the release rate, and at 9% coating level microcapsules releasing naltrexone for 50 days at a constant rate were obtained.

Cha and Pitt (1988) prepared microspheres and microcapsules of L-methadone using poly(l-lactide-co-glycolide) and poly(lactide-co-caprolactone) polymers. The desired lifetime (1 week) could be better approached using blends of different types of microspheres rather than blends of the polymers.

1.3.4.3 Antimalarial Systems

Wise *et al.* (1976,1978$_b$ and 1979$_b$) investigated the release of antimalarial drugs [sulfathiazine,2,4-diamino-6-(20-napthylsulphonyl) quinazoline and mixtures of them] from poly(lactide-co-glycolide) microcapsules and matrices. Although encouraging results were obtained from experiments in mice, these early formulations failed to reach a significant status (Lewis,1990).

Recently, Tsakala *et al.* (1988) formulated pyrimethamine microspheres and implants based on several poly(lactide-co-glycolide) polymers. Experiments *in vitro* and *in vivo* (mice) showed that the microspheres did not produce an adequate duration of drug delivery for practical application. However, promising results were obtained with the implants, as more than 3 months protection against *Plasmodium berghei* was observed in animals.

1.3.4.4 Anticancer Systems

Drug toxicity is a serious problem in cancer chemotherapy. Relatively few poly(lactide-co-glycolide) formulations

containing anticancer agents have been investigated for their potential in reducing drug toxicity.

The first to study poly(lactide-co-glycolide) anticancer systems were Yolles and coworkers (Yolles,1975; Yolles *et al.*, 1978). Cytoxan, cyclophosphamide, cis dichlorodiammine platinum and doxorubicin were combined with poly(l-lactide) to produce films and particulate systems. Although the release was not fully characterized increased effectiveness and lower toxicity for these systems, as compared to single dose administration, was reported.

Small poly(lactide) and PHB microspheres containing the antineoplastic drug cyclohexyl chloroethyl nitrosourea were prepared by a solvent evaporation process (Bissery,1984). The possibility of targeting such microspheres to specific organs, on the basis of particle size, was investigated. When these microspheres were injected intravenously in mice a 100-fold decrease in leukaemia cell survival was observed in both spleen and liver, compared to untreated controls. The 2-4μ diameter microspheres were effective against Lewis lung carcinoma in mice, being preferentially targeted to the lungs (Bissery *et al.*, 1985).

Poly(lactide) microspheres containing doxorubicin were evaluated *in vitro* and *in vivo* (Juni *et al.*, 1985). The rate of release *in vitro* after the initial burst was small, so prolonged release was obtained. Plasma levels of the drug following intra-arterial administration of the

microspheres into the liver of dogs were considerably lower than those following administration of the drug solution in saline. Microangiography revealed embolization due to the presence of microspheres in peripheral arteries in the liver. Intra-arterial chemoembolization is an effective method for treatment of solid tumours in organs (Juni *et al.*, 1985).

Studies have also been conducted with cis platin in the field of chemoembolization. Microspheres prepared by a solvent evaporation procedure were characterized *in vitro* and critical factors with regard to drug release kinetics were identified. it was concluded that factors affecting the distribution of drug crystals in the microspheres are more important in drug release than the incorporation of glycolic units in the polymer backbone (Spenlehauer *et al.*, 1986 and 1988).

A w/o emulsion method was developed for the incorporation of mitomycin C into poly(lactide) microspheres. The microspheres showed a dose-dependent drug release pattern with microspheres of higher drug loading having a faster release rate than those of lower drug loading. An enhanced antiproliferative activity against the growth of the K562 human erythroleukokemia cells was observed with the microspheres as compared with the non-formulated drug (Tsai *et al.*, 1986).

The release of cisplatin from cylindrical implants based on poly(lactide) (75% in l-lactide) and poly(dl-lactide-co-

glycolide) polymers has been investigated. The formulations were inserted in the renal parenchyma of mice. Release from the poly(lactide) implants was inadequate, but a continuous release of platinum for at least 3 weeks was observed with the poly(lactide-co-glycolide) (75:25) implants. The implantation resulted in high platinum concentrations in the kidney tissues and low plasma concentrations, compared to systemic injection (Hecquet *et al.*, 1986).

Strobel *et al.* (1987) investigated anticancer drug delivery devices which would be combined with radiation therapy or hyperthermia. The devices consisted of orthodontic wire or sutures dip-coated with drug (misonidazole or andriamycin) and poly(lactide-co-glycolide) polymers and they were designed to be inserted directly into a brain tumour. Drug release *in vitro* followed the expected first-order kinetics.

1.3.4.5 Antibiotic Systems

Antibiotic poly(lactide-co-glycolide) formulations have been investigated for the topical treatment of open wounds and periodontal disease (Dunn *et al.*, 1987; Tice *et al.*, 1984 and 1986).

Copolymers degrading relatively fast were used to prepare microspheres which would release their content within one to two weeks period. A range of antibiotic compounds, such as ampicillin anhydrate, tetracycline and chloramphenicol,

were incorporated in these microspheres using solvent evaporation or phase separation techniques (Lewis *et al.*, 1980). The microspheres were shown to release the drug according to a desired first-order fashion *in vitro*. An initial burst of release providing for the immediate perfusion of the tissues with drug was observed followed by a prolonged release which maintained a low therapeutic level of antibiotic in the tissues for the intended period. Stability and batch to batch reproducibility data for these microspheres were reported (Tice *et al.*, 1984 and 1986).

Monolithic fibres, prepared by melt-extruding blends of the drug with poly(ϵ-caprolactone) and poly(ϵ-caprolactone-co-lactide) polymers, were used to deliver tetracycline to the periodontal pocket. These fibres gave first order release over a period of 6 days, but when coated with pure polymer the release rates were essentially constant and the duration of release was significantly extended. Many of the fibres were soft and flexible and could be placed easily in the periodontal pocket to control bacterial growth. The copolymer fibres were tacky, a characteristic which should help retain the fibres in periodontal pocket (Dunn *et al.*, 1987).

A composite material prepared from hydroxyapatite and poly(dl-lactide), containing dideoxykanamycin B to prevent bacterial growth, has been tested as a substitute or a filler in the repair of bone defects. Release studies in rats showed that the concentration of the antibiotic was effectively maintained and prevented infection at the

implantation site. The rate and duration of release could be regulated by the mw of the polymer (Ikada *et al.*, 1986).

1.3.4.6 Antiinflammatory Systems

Poly(dl-lactide-co-glycolide) (85:15) microspheres containing methylprednisolone were prepared for intra-articulate administration. Experiments in rabbits with induced arthritis showed that prolonged (up to 5 months) antiinflammatory response was achieved following a single injection of microspheres (Tice *et al.*, 1985).

Poly(dl-lactide) films loaded with hydrocortisone acetate were prepared and the effects on the inflammatory and healing responses were investigated in rats using a cage implant technique. The results showed that the films inhibited all aspects of inflammation throughout the 21-days implantation period. The white cell concentration in the exudates withdrawn from cages containing hydrocortisone films were at all times lower than the white cell concentrations in the controls (empty and poly(lactide) film containing cages) (Spilizewski *et al.*, 1986).

A solvent evaporation process was used to prepare hydrocortisone loaded microspheres from poly(lactide-co-glycolide) polymers. The rate of drug release *in vitro* increased as the initial payload carried by the microspheres increased. Changing the polymer from poly(lactide) to poly(lactide-co-glycolide (65:35), whilst fixing the steroid content at 12-13%, caused a decrease in

release rate. The release data did not fit any of the common kinetics models (Cavalier *et al.*, 1986).

1.3.4.7 Other Applications

Local anaesthetic drugs, such as lidocaine, etidocaine, and bupivacaine, have been microencapsulated with poly(l-lactide) using an air suspension coating technique. The microencapsulated local anaesthetic formulations demonstrated sustained release, lower local and systemic toxicity, and longer duration of action compared to pure drug (Williams *et al.*, 1984).

In an attempt to improve patient compliance disulfiram, a drug prescribed to discourage alcoholics from drinking alcohol, has been formulated into implantable rods using poly(l-lactide-co-glycolide) polymers. The formulations, when implanted subcutaneously in rats were shown to release the drug continuously for 3 months. At necropsy, no encapsulation of the residual rods was found (Phillips and Gresser,1984).

Suzuki and Price (1985) studied the release of chlorpromazine from poly(lactide) microspheres. They concluded that the release characteristics of these microspheres can be optimized for various requirements by at least three methods: (a) by employing polymers of different molecular weight, (b) by changing the particle size of the microspheres, and (c) by changing the drug loading.

Mason *et al.* (1988) investigated the possibility of controlled delivery of neurotransmitter molecules directly to the central nervous system. Dopamine microencapsulated in poly(dl-lactide-co-glycolide) polymer was injected in the lateral striatum of rats. The animals exhibited contralateral rotations for prolonged period, whilst control animals injected with placebo microcapsules did not show any consistent rotational behaviour. Immunocytochemical studies confirmed the presence of significant amounts of dopamine containing microcapsules up to 4 weeks after implantation. Neither invasion of microcapsules from macrophages nor tissue inflammation, was observed.

1.3.4.8 Systems for the Delivery of Macromolecules

1.3.4.8.1 Delivery Systems for Polypeptides

Polypeptides of relatively low mw (less than 5000) are stable in the presence of poly(lactide-co-glycolide) excipients and their biodegradation products. They have been successfully combined with poly(lactide-co-glycolide) polymers to prepare controlled release formulations (Tice and Cowsar, 1984; Maulding ~~*et al.*~~, 1987).

Hutchinson (1982) first described the release of acid-stable polypeptides from poly(lactide-co-glycolide) matrices. Release from these systems is accomplished by two distinct mechanisms. The first involves leaching of the drug from polypeptide domains at or near the surface of the implant. The second degradation of the polymer. The

erosion of the matrix generates aqueous pores or channels through which the drug in the interior of the implant can be liberated. Because of these two mechanisms the release of polypeptides from these systems is normally biphasic. However, these two phases can be made to overlap by appropriate choice of polymer properties and polypeptide content. Thus, Hutchinson and Furr (1985) reported the continuous release of Zoladex (a Luteinizing hormone releasing hormone (LH-RH) analogue) from a poly(lactide-co-glycolide) subdermal depot over a period of 28 days both in vitro and *in vivo*.

Sanders *et al*. (1984) studied the release of nafarelin acetate (a LH-RH analogue) from poly(dl-lactide-co-glycolide) implants and microspheres. They reported similar release profiles to those reported by Hutchinson (1982), but which were described as "triphasic". The release was characterized by a "secondary" phase during which very little or no peptide was released, preceded and followed by phases of higher release rate. The duration of the "secondary" phase was found to be proportional to the mw of the copolymer and both the duration of the "secondary" phase and the total duration of release were found to be proportional to the monomer ratio (Sanders *et al*., 1986).

Recently one intramuscular injection of biodegradable controlled release nafarelin microspheres in human males, was shown to effectively suppress the testosterone plasma levels for more than one month. Fine adjustment of the

release kinetics could be achieved by modification of loading level, from 1% up to 8%, which was presumed to influence the extent of channelling caused by loss of compound, known to be a major influence in controlling diffusional release (Sanders *et al.*, 1985).

Low mw poly(dl-lactide) and compression moulding were employed to prepare needles containing a LH-RH agonist. The advantage of this formulation is that it can be easily injected under the skin and renewed conveniently. Tests in human with prostate cancer showed that the therapeutic effects could be maintained over long periods with the periodic renewal of the needles (Kaetsu *et al.*, 1987).

Ogawa *et al.* (1988a,b) described a method for the efficient entrapment of leuprolide acetate (a LH-RH analogue) in poly(dl-lactide-co-glycolide) microspheres. The release was found to be affected by the polymer composition and less by the polymer molecular weight. They aimed to produce a delivery system capable of releasing the peptide at an approximately constant rate for one month and this was best achieved by utilizing a poly(lactide-co-glycolide) (75:25) copolymer of 14000 mw.

Kwong *et al.* (1986) studied the delivery of insulin using poly(l-lactide) microspheres and pellets. They proposed that release occurred via pores in the polymer matrix. Significant initial release (burst effect) was observed with microspheres both *in vitro* and *in vivo* (rats). Pellets showed a relatively small burst effect *in vitro* and

no burst release was observed *in vivo*. The effectiveness of these insulin preparations *in vivo* was found to be dose-dependant.

1.3.4.8.2 Delivery Systems for Proteins

The preparation of controlled delivery systems for proteins cannot be accomplished using conventional formulation techniques. Proteins are high MW hydrophillic molecules which would not diffuse through the hydrophobic polymer wall of a reservoir system at a useful rate. In addition proteins can be easily deactivated during the formulation procedure (Pitt, 1990_b). Incorporation of proteins in poly(lactide-co-glycolide) systems has the additional problem of protein instability in the presence of acidic degradation products from the polymers. Nevertheless, reports of the successful combination of poly(lactide-co-glycolide) polymers with proteins have appeared in the literature.

Human serum albumin was incorporated into microcapsules, made from a 52:48 (LE:GE % mol) polymer, and could be released intact in various buffers. The rate of release was affected by the pH and ionic strength of the buffer solution and increased with an increase in the drug loading (Singh *et al.*, 1988).

The release kinetics of bovine albumin diffusion from a poly(dl-lactide) reservoir system was investigated with the long term aim of developing a multi dose pulsatile delivery

system. The albumin release profile was approximated by zero order kinetics and the rate of release was affected by the molecular weight of the polymer, the thickness and the density of the membrane. The initiation of albumin release could be delayed from a few hours to more than one month by increasing the M_v of the poly(lactide) from 6.2 X 10^3 to 140 X 10^3 and raising the concentration of the polymer coating solution from 50 to 100 $mg.ml^{-1}$. The diversity in delayed-release effect and the variations in membrane permeabilities were attributed to changes in membrane porosity and polymer morphology (Marcotte *et al.*, 1990).

Poly(lactide-co-glycolide) (75:25) microspheres containing fluorescein isothiocyanate-labelled bovine serum albumin (FITC-BSA) and fluorescein isothiocyanate-labelled horseradish peroxidase (FITC-HRP) were prepared by a modified solvent evaporation method using a double emulsion. The preparation method was gentle and maintained the enzyme activity and the protein solubility. The incorporation of the FITC-HRP into the poly(lactide-co-glycolide) microspheres was found to increase its stability. Different release profiles and rates could be achieved by changing the mw of the polymer or modifying factors in the preparation procedure (Cohen *et al.*, 1991).

1.4.4.8.3 Delivery Systems for Vaccines

Most vaccines require two or three primary immunizations, followed by a booster for optimum immune response. A one

time vaccination would eliminate patient compliance problems, and it would reach a greater percentage of the target population (Singh *et al.*, 1991).

A method for delivering antibodies or antigens to the female reproductive tract has been described. Because systemic antibodies are not secreted by the internal reproductive organs, the immunization levels of these organs cannot be increased by systemic administration of either antibodies or antigens, but rather must be increased by local administration of antibodies or antigens to the female reproductive organs. Monolithic or reservoir poly(lactide-co-glycolide) microparticles 120-60μ size, containing antigens, such as *Neisseria gonorrhoea* and Herpes virus, or antibodies are deposited in the vagina allowing the natural transport mechanism of the internal organs to convey the microparticles into the uterus. Furthermore, microparticles containing menstrual cycle regulating hormones (estradiol or progesterone) could be administered together with those containing antigens or antibodies, so that the hormones would induce the necessary secretory changes in the endometrium of the cervix and would promote the contractile activity of the cervix necessary for microparticles transport. Tests with rabbits showed that the intravaginal installation of these microparticles caused immunization against the various antigens administered (Beck *et al.*, 1988).

Gilley *et al.* (1988) developed poly(lactide-co-glycolide) microspheres that target the Peyer's patches

(lymphrentricular follicles on the gastrointestinal tract of man) and release antigens at controlled rates. It was noticed that microspheres less than 5μ in diameter traverse the Peyer's patches and enter the circulation, whilst microspheres 5 to 10μ in diameter remain inside the Peyer's patches for extended periods (months). When administered orally in mice, microspheres less than 5μ containing staphylococcal enterotoxin B (SEB) or pneumococcal polysaccharide were shown to induce significant systemic immunity. The SEB containing microspheres of 5 to 10μ size caused a substantial mucosal anti toxin response in the saliva, gut, and lung secretions.

Diphtheria toxoid has been microencapsulated using poly(dl-lactide) without loss of its immunogenicity. The microcapsules when injected subdermally to mice elicited antibody titers comparable to those obtained with the conventional three-dose injection of diphtheria toxoid, over 75 days (Singh *et al.*, 1991).

1.4 Purpose of the Work

The advantages of employing biodegradable polymers in the fabrication of sustained drug release systems have been discussed in the preceding introduction. The most successful biodegradable polymers at this time appear to be the poly(lactide-co-glycolide) polymers.

Commercially poly(lactide-co-glycolide) polymers are not available at the present in an adequate range, or with adequate characterization. This is mainly because the preparation process affects their chemical, physical and mechanical properties in a way that is not well understood and prevents the preparation of products with consistent properties. Also there appear to be no reports in the literature regarding their application in the preparation of heterogeneous compressed matrices, which is one of the most common practical techniques to achieve sustained drug delivery.

The present work has been structured, under the following headings, to investigate the suitability of poly(lactide-co-glycolide) polymers in the preparation of controlled release matrix tablets:

1. Investigation of preparative variables affecting the properties of poly(lactide-co-glycolide) polymers as matrix forming material.

2. Preparation and characterization of poly(lactide-co-glycolide) powders for tableting.

3. Preparation and characterization of poly(lactide-co-glycolide) matrix tablets.

Table 1 Mark-Houwink Parameters for Poly(lactide-co-glycolide) polymers in chloroform

Reference	Polymer	average MW	K X 10^4	α
Schindler and Harper (1979)	poly(l-lactide)	M_n	5.45	0.73
Schindler and Harper (1979)	poly(dl-lactide)	M_n	2.21	0.77
Wise *et al.* (1979)	90:10 (P-LE:GE%mol)	M_w	1.04	0.75
Rak *et al.* (1985)	poly(dl-lactide)	M_n	6.60	0.67
Rak *et al.* (1985)	poly(dl-lactide)	M_w	6.06	0.64
Pit and Gu (1987)	70:30 (l-LE:GE%mol)	M_n	9.96	0.66
Deasy *et al.* (1989)	poly(l-lactide)	M_w	0.30	0.94

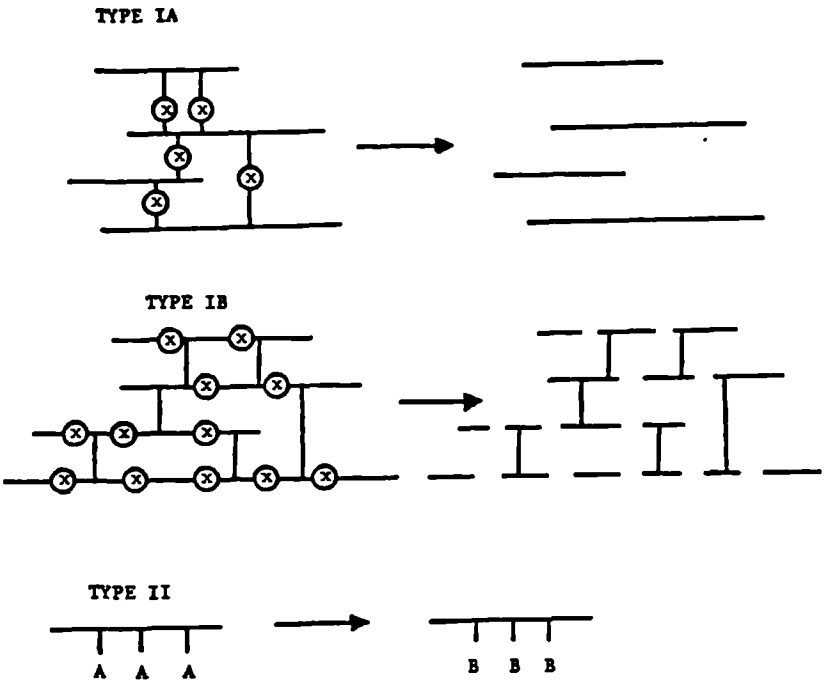


FIGURE 1. Schematic representation of degradation mechanisms.

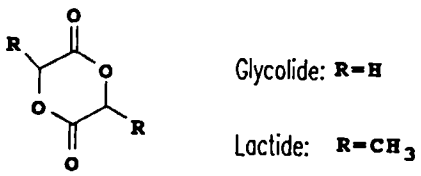
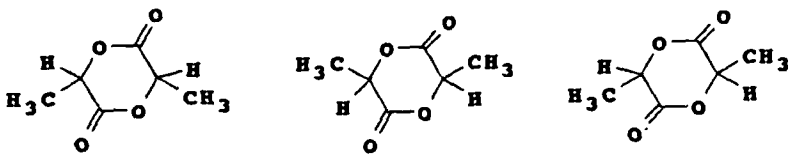
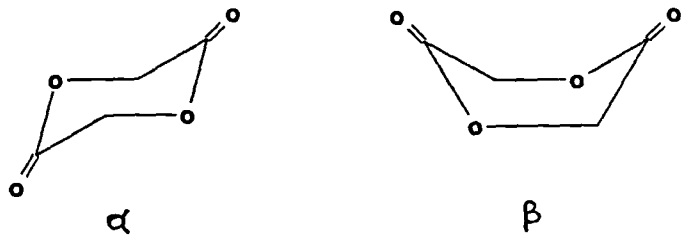


Fig.2 Chemical structure of glycolide and lactide



L- D- meso-

Fig.3 Lactide diastereoisomers.



α β

Fig.4 Configurations of glycolide.

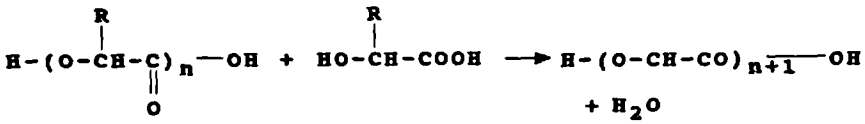


Fig.5 Step growth polymerization of α-hydroxy acids (R is H or CH3 for glycolic or lactic acid respectively).

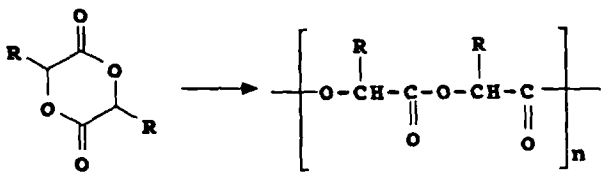


Fig.6 Ring opening polymerization of lactide/glycolide (R is H for glycolide and CH3 for lactide).

2. PREPARATION AND CHARACTERIZATION OF POLY (LACTIDE-CO-GLYCOLIDE) POLYMERS

2.1 Introduction

A systematic study of the synthesis of poly(lactide-co-glycolide) polymers appears to be lacking in the literature Most preparative variables affecting the properties of the produced polymer have been identified and their effects have been analyzed in a rather empirical manner. Little, if any, effort has been made to correlate the effects of changing the polymerization conditions with the mechanism of polymerization, probably because the mechanism of polymerization has not as yet been fully elucidated. This may account for the contradictory findings for the effect of changing the polymerization conditions on the properties of the synthesized polymer. Thus, an increase in the amount of organometallic catalysts in the polymerization mixture has been reported to cause an increase in the molecular weight of the produced polymer (Chawla and Chang, 1983), a decrease in the molecular weight (Jacobson, 1970; Deasy et al., 1989), or to have no significant effect (Rak et al., 1985). Furthermore, it appears that, so far, no attempt has been made to correlate the polymerization conditions to the composition and microstructure of the resulting polymer, despite the significance of these characteristics on the polymer properties.

In this chapter a detailed study of the synthesis of poly(lactide-co-glycolide) polymers, from a pharmaceutical viewpoint, has been undertaken. The effect of several preparative variables on the properties of the polymer, such as molecular weight and composition, and on the yield

of polymerization has been investigated. The microstructure (sequence of monomers in the copolymer chains) of the resulting polymers has also been considered

2.2 Investigated Variables of Polymer Synthesis

The effect of the following preparative variables on the properties of the resulting polymers was investigated:

I. type of catalyst: two catalysts were used, stannous octoate and antimony trifluoride.

II. concentration of catalyst: a lower catalyst-level series, i.e. 0.~~05~~ 0.05, 0.02, 0.03, 0.05, and 0.1% w/w of the monomers mixture was employed at high polymerization temperatures, whilst higher catalyst-level series, i.e. 0.02, 0.05, 0.1, 0.2, and 0.5% were employed at low polymerization temperatures.

III. concentration of co-catalyst: lauryl alcohol at 0.01 and 0.05% w/w of the monomers mixture was used.

IV. temperature of polymerization: two reaction temperatures were applied, a low (130^{o}C) and a high (190^{o}C).

V. time of polymerization: four polymerization periods were compared, i.e., 1, 2, 4 and 8 hours both at low and high polymerization temperatures, using optimum catalyst levels.

2.3 Materials and Methods

2.3.1. Materials

dl-Lactic acid (technical, 80% solution in water) and glycolic acid (analar) were purchased from Aldrich. Reagents and solvents used in the preparation and characterization of polymers are listed in Table 2.

2.3.2 Methods

2.3.2.1 Synthesis of polymers

The synthesis of poly(lactide-co-glycolide) polymers was based on the method described by Gilding and Reed (1979).

2.3.2.1.1 Preparation of dl-lactide and glycolide

Lactide synthesis involves the condensation of lactic acid to low molecular weight poly(lactic acid) which is then depolymerized to the cyclic dimer (reactions 1, 2 in Fig. 7).

600 g of 80% dl-lactic acid solution in water and 1.44 g of antimony trioxide were heated at 140^{o} and magnetically stirred in a 1000 ml round bottom flask, fitted with a distillation head and condenser. When the rate of water elimination fell a water aspirator was connected and the temperature increased gradually to 180^{o} C. When no further water was evolved an air condenser was substituted for the water type and an oil pump for the water aspirator. A clean receiver cooled in liquid nitrogen was attached. The

temperature was then raised to 250° C and the vacuum increased to 0.1-0.5 mm Hg. Lactide sublimed and distilled over as a pale yellow waxy solid. The yellow colour was removed by washing with chloroform and, after two recrystallizations from ethyl acetate and one from acetone, a shiny white crystalline material was obtained with a melting point of 124° C (measured using a Gallenkamp, England, melting point apparatus). Glycolide was synthesized using the same procedure as with lactide. The purified shiny white crystalline material had a melting point of 82° C.

Both lactide and glycolide were stored in evacuated desiccators over silica gel until used.

2.3.2.1.2 Polymerization of lactide and glycolide

Poly(lactide-co-glycolide), in 5 g batches, were synthesized via the ring opening polymerization of lactide and glycolide (reaction 3 in Fig. 7).

The polymerization mixtures consisting of monomers (lactide and glycolide) at predetermined weight ratios, catalyst, and co-catalyst (if used) were put into thick-walled glass tubes which had previously been rinsed with acetone and dried overnight. Stannous octoate is a viscous liquid and the small quantities required could not be accurately measured. Therefore, it was dissolved in hexane to form stock solutions of known concentration and the appropriate volume of these solutions was each time transferred into

the polymerization tubes. The tubes, after flushing with nitrogen, were evacuated, sealed, and heated in an oven for specified periods of time.

The resulting glassy, colourless to pale green solids were dissolved in tetrahydrofuran to give approximately 20% w/w solutions. These solutions were precipitated in excess distilled water and the polymers collected as white cocoons on glass rods. The purified polymers were dried in a vacuum oven at 40° C until constant weight.

2.3.2.2 Characterization of polymers.

2.3.2.2.1 Molecular weight determination

The molecular weight of the samples was determined by viscometry. The flow time of 1% w/v solutions of the samples in chloroform was measured using our Ubbelhode suspended level viscometer (size A). The temperature was maintained at 25° C using a Bridge Control Series II water bath (Townson and Mercer Ltd., England). The inherent viscosity (iv) was calculated from the formulae:

$$iv = \frac{\ln n_{rel}}{C} = \frac{\ln t12/t1}{C} \qquad \text{Equation 11}$$

where n_{rel} is the relative viscosity, t12 is the flow time of the polymer solution, t1 is the flow time of the solvent, and C is the concentration of the polymer solution.

2.3.2.2.2 Identity and Purity of Polymers

The identity and purity of the polymers was investigated by IR and ^{1}H-NMR spectroscopy. The ^{13}C-NMR spectra, recorded primarily for the investigation of the polymer microstructure, could provide further evidence for the purity and identity of the synthesized polymers.

The IR spectra were determined in an SP-800 spectrophotometer over the range 4000-600 cm^{-1}. KBr discs, containing approximately 1% w/w of the compound being examined were used, with air as reference.

The ^{1}H-NMR spectra were recorded with a Perkin Elmer R32 spectrometer (England) operating at 90 MHz. The samples were dissolved in $CDCl_3$ and tetramethyl silane (TMS) was used as internal standard.

2.3.2.2.3 Determination of Polymer Composition

The composition of the samples was determined by comparing the integrals of the surface of the peaks assigned to the lactic unit backbone proton, $>CH^{*}-CH_3$, and to the glycolic unit protons $-O-CH_2^{*}-CO-$ (Fig. 8).

2.3.2.2.4 Investigation of Polymer Microstructure

The microstructure of certain samples, prepared under different polymerization conditions, was investigated using high field (62.8 MHz approximately), ^{13}C-NMR spectra,

decoupled from protons, recorded in a Bruker WM 250 spectrometer. The polymers to be examined were dissolved in $CDCl_3$ and deuterated dimethyl sulfoxide (DMSO), and TMS deuterated was used as internal standard. Expansion of the spectra was used to obtain information for the fine structure of the carbon resonance.

2.3.2.2.5 Investigation of Polymer Morphology

Differential scanning calorimetry (DSC) was used to study the effect of the preparative variables on the morphology of the polymers. The thermograms were obtained with a Du Pont 910 instrument coupled to a Du Pont 9000 analyzer at a heating rate of 10^{o} C/min. Two runs were made with each sample, the first serving as a technique to provide a standard thermal history for all samples. The DSC instrument was calibrated using indium (melting point 156.4^{o}C).

2.4 Results and discussion

2.4.1 Preparation and characterization of polymers

During preliminary experiments the recrystallization of lactide/glycolide was found to significantly affect the polymerization. When crystallization was induced by an ice-water bath, small crystals of lactide and glycolide were obtained. These crystals did not give reproducible polymerization behaviour and resulted in low molecular weight polymers. However, when crystallization was allowed

to occur slowly at ambient temperature, large crystals of lactide and glycolide were obtained which gave reproducible polymerization and resulted in high molecular weights polymers. This phenomenon could be attributed to the difference in specific surface area between large and small crystals. These cyclic diesters are sensitive to traces of atmospheric moisture, being converted during storage to acidic oligomers which cause erratic polymerization behaviour. The small crystals, having larger specific surface area, were more labile to moisture. Moreover, when the crystallization of glycolide proceeds at a low temperature, the form which is more sensitive to moisture is produced (Frazza and Schmitt, 1971).

Preliminary polymer syntheses also indicated that polymerization temperatures in excess of 200^{o} C caused polymer decomposition, when a 4 hours polymerization time was used, giving a brown colour to the products.

The identity and purity of the synthesized polymers was investigated with ^{1}H-NMR and IR spectroscopy.

A typical ^{1}H-NMR spectrum is shown in Fig. 8. The multiplet at 1.55 ppm was assigned to the methyl protons of the lactic acid units >CH-CH_3*, the doublet at 4.80 ppm was assigned to the protons of glycolic acid units - CH_2* - and the multiplet at 5.20 ppm was assigned to the backbone protons of the lactic acid units >CH*-CH_3. Overlapping of the signals from the l- and d- configurations of lactic

acid units in the P-dl-LGA copolymers results in the multiplets at 1.55 and 5.20 ppm. If only one lactic acid antipode had been used to prepare the copolymers the multiplets at 1.55 and 5.20 ppm would be a doublet and a quartet respectively.

A typical IR spectrum of the copolymers prepared in this work is shown in Fig. 9. The major peaks assigned to the structure of poly(lactide-co-glycolide) copolymers are: 3500 cm^{-1} (O-H stretching), 2950 and 3000 cm^{-1} (C-H stretching), 1750 cm^{-1} (ester c=O stretching), 2450 cm^{1} (C-H bending) and 1100 cm^{-1} (C-O stretching). The IR and ^{1}H-NMR spectra showed that the copolymers produced were pure and genuine.

The polymerization of lactide and glycolide has been shown to be a chain reaction (Dittrich and Schulz, 1971). This type of polymerization often proceeds at a very high rate which increases the difficulty of obtaining reproducible results (Billmeyer, 1984). The reproducibility of polymerization in the present work has been checked by producing two batches of 90:10 (initial lactide:glycolide weight ratio) copolymer under identical conditions (0.03% w/w stannous octoate, 290^{o} C for 1 hour). The results obtained (iv_1 = 0.459, $yield_1$ = 56.0% and iv_2 = 0.500, $yield_2$ = 46.3%) were regarded as showing a satisfactory reproducibility.

2.4.2 Mechanism of Polymerization

The polymerization of lactones is a chain reaction which can be effected by both anionic and cationic catalysts. Cherdron et al. (1962) proposed that in both anionic and cationic polymerization chain growth occurs via alkyl-oxygen cleavage of the lactone, i.e. by cleavage of the bond between the carbonyl carbon and the heterocyclic oxygen (Fig. 10 reactions 1 and 2). However, recent research has provided evidence that polymerization initiated by cationic catalysts proceeds via cleavage of the alkyl-oxygen bond (Fig. 10 reaction 3) (Kricheldorf et al., 1986). Thus, polymerization of lactide/ glycolide using antimony trifluoride as catalyst will be cationic, proceeding either by alkyl or alkyl oxygen cleavage (Fig. 10).

A co-ordinate mechanism for the polymerization of lactide with organometallic catalysts, such as diethyl zinc or triethyl aluminium, has been proposed (Dittrich and Schultz, 1971). A similar mechanism may operate when the polymerization is initiated with stannous octoate, and a possible reaction scheme is given in figure 11. The initiation involves attack by a lone pair of electrons on the heterocyclic lactide (glycolide) oxygen on the vacant d orbitals of tin, and a nucleophilic addition to the lactide carbonyl group (analogous to the nucleophilic attack of hydroxylions during alkaline ester hydrolysis). The lactide ring is then cleaved to give an open product which reacts with another lactide (glycolide) molecule to form the active species A. Propagation proceeds via the

co-ordination of lactide (glycolide) molecules at both sides of the tin atom (since the active intermediate possess two co-ordination sites) in a similar manner to the initiation step. Since the termination step usually involves transfer to some species not essential to the reaction, polymerization with carefully purified reagents may lead to systems in which termination is lacking, called "living polymers" (Billmeyer, 1984). The co-ordinate solution polymerization of lactide using diethyl zinc has been reported to result in a living polymerization system (Dittrich and Schultz, 1971). The anionic solution polymerization of glycolide has recently been shown to follow a living polymerization mechanism (Braun and Kohl, 1986). Nevertheless, traces of lactoyllactic acid formed by the hydrolysis of lactide, or traces of moisture, may function as chain transfer agents causing termination of the polymerization.

2.4.3 Effect of Catalyst Type

Lewis acids and organometallic compounds are two types of catalyst that have been reported as particularly effective in the ring opening polymerization of lactide and glycolide. Antinomy trifluoride is a widely used representative of the first category and stannous octoate of the second (Lowe, 1954; Chujo *et al.*, 1967; Schindler *et al.*, 1977; Gilding and Reed, 1979; Deasy *et al.*, 1989). The results obtained when using these catalysts are given in table 3. Under both polymerization conditions stannous octoate was far more effective, resulting in polymers which

had from 3 to 9 times, depending on the polymerization conditions, greater molecular weight (iv) than the polymers synthesized using antinomy trifluoride (table 3). It would appear that organometallic type catalysts are more effective than Lewis acids in polymerizing lactide and glycolide. Polymers produced using antimony trifluoride were yellowish, brittle, granular materials, whereas polymers synthesized using stannous octoate were white, tough, fibrous masses.

The 70:30 (initial LE:GE w/w ratio) polymers synthesized using antimony trifluoride had higher molecular weights than the 90:10 synthesized using the same catalyst (table 3). It appears, therefore, that antimony trifluoride is a more effective catalyst for the polymerization of monomer mixtures rich in glycolide. Chujo *et al.* (1967) reported that Lewis acids were effective catalysts for the polymerization of poly(glycolide) and poly(lactide-co-glycolide) with high glycolide contents and the results obtained here appears to confirm their report. Since stannous octoate was found to be more effective, this catalyst was chosen for the remainder of the work.

2.4.4 Effect of Catalyst Level

The effect of catalyst amount (% w/w) of the polymerization mixture) on the polymer molecular weight under two reaction temperatures is shown in Figs. 12 and 13. At both temperatures there was an initial sharp increase in molecular weight at the low catalyst levels, but this

passed through a maximum before falling at higher levels of catalyst. The results also show that the effective catalyst concentrations depend on the temperatures at which the polymerization proceeds.

The effect of catalyst concentration on the percentage yield of the reaction is shown in Table 4. The yield was affected less by the polymerization temperature than by the catalyst level. The change in yield with respect to catalyst level followed the same pattern as the change in molecular weight. There was a sharp initial increase in the yield, but this reached a maximum at the effective catalyst level before falling at higher catalyst levels. High conversions were generally obtained, especially at optimum catalyst concentrations (where optimum means the catalyst levels resulting in polymers of the highest MW at a given polymerization time and temperature). It appears that the amount of catalyst required for polymers with high molecular weights coincides with the amount of catalyst resulting in a high yield. The optimum catalyst levels were 0.03 and 0.1% w/w at 190^{o}C and 130^{o}C respectively (Figs. 12 and 13, Table 4).

Dittrich and Schulz (1971) reported that the rate of polymerization of lactide is proportional to the monomer and catalyst (active species A in Fig 11) concentration. Consequently, at very low catalyst levels the reaction rate will be very small, leading to low MW polymers and a correspondingly low yield. At higher catalyst levels the reaction rate increases and high MW and percentage yield

are obtained. This corresponds to the ascending part of the curves in Figs.12 and 13. A further increase in catalyst levels causes a too rapid reaction rate, resulting in a sudden MW build up followed immediately by a MW decline indicating that depolymerization has taken place.

A special case of transesterification reaction called "back biting") has been reported to occur during the cationic polymerizations of lactones, causing degradation of the polymer being produced (Kricheldorf *et al.*, 1986). Transesterification reactions have been shown to occur during the polymerization of lactide (Dittrich and Schulz, 1971; Chabot *et al.*, 1983), and it is, therefore, probable that "back biting" depolymerization reactions occur during the polymerization of lactide and glycolide. A possible mechanism for the back biting reactions is given in figure 14. This involves the attack by a lone pair of electrons from a carbonyl oxygen on the vacant orbital of a tin atom in the same polymer molecule and a nucleophilic attack on the same carbonyl group leading to cleavage of the chain into two segments. An increase in the catalyst to monomer ratio would increase the polymer molecules to monomer ratio and lead to an increased probability of "back biting" reactions taking place; especially towards the closing stages of polymerization, when the proportion of monomers in the polymerization mixture has greatly been decreased. This probably accounts for the decrease in polymer molecular weight observed when the catalyst levels increased beyond the optimum for a given set of polymerization conditions. (Figs 12 and 13).

Chawla and Chang (1986) used tetraphenyl tin as catalyst and found that, for 5 hours polymerization at 170°C, and increase in catalyst level in the range of 0.01% to 0.046% caused an increase in poly(lactide) molecular weight. Deasy *et al.* (1989) used stannous octoate and found that for 6 hours polymerization at 160°C, and increase in the catalyst levels from 0.19 to 0.95% caused a decrease in poly(lactide) MW. It would appear that the results reported by Chawla and Chang (1986) correspond to the initial portion of the kinetics behaviour observed in this study (ascending part of the curves in Fig. 13) whilst the range of catalyst levels used by Deasy *et al.* (1989) were in excess of the optimum level and correspond to the descending part of the curves in Fig. 12.

Higher mw polymers were obtained at the lower temperature level of 130°C (Figs. 12 and 13). This may be attributed to the increased rotational and folding mobility of the linear polymer molecules at the higher temperature, which increasing the probability of "back biting" depolymerization reactions resulted in a decline of the polymer molecular weight.

Polymers with an inherent viscosity in chloroform of 0.2 or less, which were prepared using very low catalyst levels, are yellowish, granular, brittle materials that could readily be powdered by grinding. Polymers with higher iv are fibrous and tough and could not be powdered by grinding. The shorter the chains of a linear polymer the higher the probability that these chains would assume

ordered ("crystalline like") structures and conversely the longer chains of a linear polymer could be aligned parallel to each other forming a fibrous structure and this might explain the differences in the texture between low and high MW polymers.

2.4.5 Effect of Co-Catalyst

Small amounts of alcohols, such as lauryl alcohol, have been reported to act as accelerators for the reaction at the onset and as mw controllers, preventing depolymerization, in the later stages of polymerization (Schmitt *et al.*, 1969). However, the inclusion of lauryl alcohol in the polymerization mixture has recently been reported to have no evident effect (Rak *et al.*, 1985). When lauryl alcohol was incorporated in the polymerization mixture, increasing the co-catalyst level caused both a lowering of molecular weight and percent conversion (Table 5). Thus, the incorporation of 0.05% w/w lauryl alcohol resulted in a ~30% decrease in the molecular weight of the resulting polymer and a 10% decrease in the conversion. This result shows that the molecular weight can be regulated to lower values by the incorporation of small amounts of lauryl alcohol in the polymerization mixture.

Frazza and Schmitt (1971) proposed that the mechanism of glycolide polymerization by tin catalysts in the presence of alcohol is cationic. The rate determining step is considered to involve the ring opening addition of an hydroxyl group from either the alcohol, or the growing

chain, to the protonated glycolide molecule. This gives an open chain adduct which is protonated on the penultimate ester group. The adduct then undergoes a rapid proton exchange with uncharged monomer and the process is repeated to build up the chain. Protons can be generated by decomposition of the catalyst, or through its reaction with the alcohol (Fig. 15).

The decrease in polymer molecular weight with an increase in lauryl alcohol content of the polymerization mixture (Table 5) may be attributed to the increased probability of alcohol molecules interfering with the proton exchange (Fig. 15) by competing with the glycolide (lactide) molecules for the protons of the growing polymer chains. The alcohol involvement in the proton exchange, which becomes more significant as the polymerization proceeds and the glycolide (lactide) is depleted, inhibits further chain growth resulting in lower molecular weight polymers.

2.4.6. Effect of Polymerization Time

The effect of polymerization time was studied at both 130^{o}C and 190^{o}C using the optimum catalyst concentrations (Figs. 16 and 17). The molecular weight continued to increase throughout the reaction (up to 4 hours) indicating that the polymerization was not a chain reaction in the kinetic sense. This becomes more obvious when the inherent viscosity is plotted against percentage yield. The molecular weight continued to increase at conversions

higher than 90%, regardless of the polymerization temperature (Fig. 18).

At optimum catalyst levels the conversion remained essentially constant or decreased slightly after 4 hours polymerization. At optimum catalyst levels high % yields were obtained after 4 hours polymerization (Table 4 and Fig. 17), indicating that the polymerization had essentially been completed within the 4 hours period and, therefore, only "back biting" depolymerization reactions could probably occur after that period, causing the observed decrease in the molecular weight of the resulting polymers (Fig. 16). When a lower than optimum level of catalyst was employed the molecular weight and % yield were still increasing after the 4 hours period (Figs. 16 and 17).

The polymerization has been reported to be a first order reaction with respect to monomer. By fitting the data of Fig. 17 to first order equations the polymerization rate constants were calculated from the slope of the regression lines. For polymers prepared using optimum catalyst conditions the data up to 4 hours, and for polymers synthesized using sub-optimum catalyst levels, the data up to 8 hours, were used in the determination of the rate constants. These constants indicate that the rate of polymerization increased significantly with an increase in the polymerization temperature or the proportion of catalyst (Table 6).

The time of polymerization may be expected to affect the composition of the resulting copolymer because glycolide, being more reactive, will be preferentially polymerized in the initial stages, whilst lactide will be incorporated to an ever increasing extent as the glycolide is depleted. The composition of copolymers produced using different reaction times is given in Table 7. The proportion of glycolic acid units in the copolymer falls as the time of polymerization increases. However, the composition of the copolymers remains essentially constant at polymerization times longer than 4 hours.

It appears that for a given polymerization temperature when efficient amounts of catalyst are used, the optimum polymerization time is 4 hours since the polymer molecular weight falls at longer polymerization periods whilst the conversion does not increase (Figs. 16 and 17). It is of equal importance that the composition of the copolymers appears to stabilize after 4 hours polymerization, so that polymers with consistent properties can be prepared employing a 4 hours polymerization period (Table 7). When sub-efficient catalyst levels are used longer polymerization times are required (Figs. 16 and 17). With higher than optimum conditions of catalyst the reaction proceeds too rapidly and shorter polymerization times have to be employed to produce the same degree of polymerization.

2.4.7 Effect of Preparative Variables on the Microstructure and Morphology of the Polymers

The difference in reactivity between the two monomers could have a significant effect on the microstructure of the copolymer. It has been estimated that the reactivity of glycolide is 2.8 whereas the reactivity of lactide is 0.2 at 200°C, which implies that a chain with a growing glycolide end has a 3:1 preference for adding another glycolide, whereas an equivalent chain with a growing lactide end has a 5:1 preference for glycolide (Gilding and Reed, 1979). It is to be expected, therefore, that copolymers containing blocks of glycolic acid units will be produced rather than copolymers of a random structure. The microstructure of a copolymer can affect its solubility in organic solvents, its rate of hydration and its rate of biodegradation. Thus, Dunn *et al.* (1988) reported that a 50:50 (LE:GE%mol) copolymer with a random structure had a better solubility in organic solvents and a higher degradation rate *in vitro* than a 50:50 block copolymer. The monomer sequence in the copolymers prepared in this study was investigated using high field ^{13}C-NMR spectra. A typical ^{13}C-NMR spectrum, from a 90:10 (LE:GE initial w/w ratio), is shown in Fig. 19 and it can be interpreted as follows: the peak at (approximately) 16.7 ppm corresponded to the lactic acid's methyl carbon atom, >CH-*CH$_3$, the peak at 60.7-60.9 ppm corresponded to the glycolic acid's methylene carbon, -O-*CH$_2$-CO-, the peak at 69.0-69.2 ppm was assigned to the lactic acid's methine carbon, >*CH-CH$_3$, the peak at 166.4 ppm was assigned to the glycolic acid's

carbonyl carbon, -O-*CO-CH_2-, and the peak at 169.4-169.6 ppm corresponded to the lactic acid's carbonyl carbon, -O-*CO-CH-CH_3. The signals at 0 and 77 ppm approximately were assigned to the internal standard (TMS) and the solvent ($CDCL_3$) respectively. The solvent resonance showed up as three lines due to the spin-coupling of carbon atom to deuterium.

Since racemic lactide was used to prepare the polymers, the fine structure of the spectrum results from both compositional and configurational effects. The glycolic acid's carbonyl carbon signal showed up as a singlet, but expansion of the spectrum revealed the existence of shoulders on the peak, implying that there might be glycolic acid's carbonyl carbons with slightly different chemical shift (Fig. 20). When DMSO, which is more polar than $CDCl_3$, was used as solvent this signal appeared as two singlets at 166.5 and 166.5 ppm indicating that two slightly different molecular environments for the glycolic acid's carbonyl carbon occurred (Fig. 21).

In Fig. 22 the spectrum in DMSO of a 70:30 (initial LE:GE w/w ratio) is shown. The glycolic carbonyl signal was again two singlets but the intensity of the signal was higher because of the higher proportion of glycolide units in the polymer. In all samples examined the glycolic carbonyl resonance had the form shown in Figs. 21 and 22 irrespective of composition, temperature and time of polymerization.

In poly(lactide-co-glycolide) copolymers the possible molecular environment for the glycolic acid's carbonyl carbon are G*GG, G*GL and L*GG (G = glycolic acid unit, L = lactic acid unit) and, consequently, in the spectrum of a random copolymer the resonance of this carbon should appear as three lines. However, because glycolide is more reactive, blocks of glycolide separated by single lactide units were probably formulated during copolymerization, so that the concentration of G*GL and L*GG sequences was low and their signals indistinguishable. Consequently the glycolic acid's carbonyl signal appeared as two peaks instead of three (Figs. 21 and 22). Hutchinson (1982) reported that the signal of this carbon atom appeared as two singlets in the spectrum of heterogeneous copolymers (polymers having molecules rich or poor in glycolide prepared, for example, by mixing polymers with different lactide/glycolide content) in DMSO.

The lactic acid's carbonyl carbon signal (Fig. 20) was very similar to the signal of the same carbon atom in the spectrum of poly(dl-lactide) in $CDCl_3$, recorded by Chabot *et al.* (1983).

In the spectrum of a random copolymer the resonance of the lactic carbonyl would be expected to differ significantly from the resonance of the same carbon in the spectrum of a homopolymer due to the different molecular environments this carbon can exist in the copolymer molecules.

Thus, from the form of the glycolic and lactic carbonyl signals it could be deduced that block poly(lactide-co-glycolide) polymers have been prepared in this work. This result also indicates that the transesterification reactions - which have been shown to occur during lactide polymerization - did not result in detectable redistribution of glycolide units in the copolymer molecules.

Morphology is an important characteristic of poly(lactide-co-glycolide) polymers affecting their biodegradation rate and mechanical strength (Vert *et al.*, 1981 and 1984). Amorphous polymers might be preferable in drug delivery since they can form monophasic matrices with homogeneous dispersion of the active ingredient.

The morphology of the polymers prepared in this study was investigated by DSC. Because racemic lactide was used to synthesize the polymers, a random arrangement of the asymmetric centres which prevents the polymer chains to assume ordered structures result, and all polymers were found to be amorphous, showing only glass transition temperature, Tg (Fig. 23). An increase in the molecular weight of the polymer increased the Tg probably because of the increased entanglement between the polymer molecules imposing restrictions to chain mobility as the mw of the polymer increases. An increase in the lactide content also caused an increase in the polymer Tg which may be attributed to the increased difficulty for chain rotation and translation caused by the increased number of methyl side groups in the polymer chains (Table 8).

The free volume, chain mobility and permeability of polymers dramatically increases at temperatures above their Tg and a decrease of poly(lactide-co-glycolide) Tg to values close to body temperature would affect its biodegradation rate, since the polymer would be more permeable to water and would be able to accommodate larger quantities of water. For the same reasons the rate of drug release from a polymer will be different depending on if the polymer is above or below its Tg in the physiological environment. Tg values as low as 37^{o}C were observed with low mw polymers (Table 1). Moreover, Omelczuk *et al.* (1990) observed that very low mw poly(lactide) samples had Tg values below 30^{o}C. These data imply that low mw poly(lactide-co-glycolide) polymers, particularly those with high glycolide contents (Table 8) can be close to or above their Tg in the physiological environment and would exhibit different biodegradation and drug release properties than high MW polymers. Furthermore, big differences in Tg could bring about differences in the compaction behaviour of the polymers since polymers with low Tg will exhibit increased consolidation during compression due to increased plastic flow at the points of contact between the particles. This mechanism could be considered similar to the asperity melting found by York and Pilpel (1973) on low melting point fatty acids.

TABLE 2: List of Reagents and Solvents used in the Preparation and Characterization of Poly(lactide-co-glycolide) Copolymers

REAGENT/SOLVENT	SOURCE	GRADE
acetone	FSA	analar
antimony trifluoride	Aldrich	analar
antimony trioxide	Aldrich	analar
chloroform	FSA	analar
ethyl acetate	FSA	analar
hexane	FSA	HPLC
lauryl alcohol	BDH	GPR
stannous octoate	Sigma	analar
tetrahydrofuran	FSA	SLR

TABLE 3 Effect of type of Catalyst on the Inherent Viscosity (dl/g) of the Copolymers

Reaction conditions[a]	Stannous Octoate		Antimony Trifluoride	
	90:10[b]	70:30	90:10	70:30
0.03% catalyst, 190°C	0.698	0.593	0.185	0.191
0.1% catalyst, 130°C	0.805	0.640	0.090	0.141

[a]=4h polymerization
[b]=Initial lactide:glycolide w/w ratio.

TABLE 4: Effect of Catalyst Concentration on Percentage Yield of Polymerization

	% Stannous Octoate	90:10[a]	70:30
130°C (4h)	0.02	21.0	66.6
	0.05	84.6	84.6
	0.1	94.5	97.6
	0.2	96.3	95.0
	0.5	86.1	88.2
190°C (4h)	0.005	8.0	32.0
	0.02	93.1	81.2
	0.03	98.0	92.4
	0.05	90.3	73.5
	0.1	84.0	70.0

[a]Lactide:glycolide initial w/w ratio

TABLE 5: Effect of Co-catalyst Concentration on the Molecular Weight (iv) of the Copolymer and on the percentage yield of the polymerization.

% Lauryl alcohol (w/w)	iv (dl/g)	% Yield
0	0.663	98.3
0.001	0.612	91.4
0.05	0.462	88.3

Polymerization conditions: 0.03% stannous octoate, 4h, 190°C, 90:10 initial lactide:glycolide ratio (w/w)

TABLE 6: Polymerization Rate of a 30:10 (Initial Lactide: Glycolide Weight Ratio) Polymer

CATALYST LEVEL (% WEIGHT)	T(^{o}C)	t (hours)	RATE CONSTANT (HOURS^{-1})	r
0.03	130	8	0.415	0.9831
0.03	190	4	2.418	0.9892
0.10	130	4	1.658	0.9910

The catalyst was stannous octoate. The rate constants were calculated by fitting the % amount of monomer vs time data to first order equations (r = correlation coefficient)

TABLE 7: Effect of Polymerization Time on the Copolymer Composition

Time (h)	% Glycolic acid units	
	0.03% Catalyst 190^{o}C	0.03% Catalyst 130^{o}C
1	17.5	-
2	16.2	21.6
4	13.9	17.7
8	13.9	16.9

Starting composition 90:10 w/w lactide:glycolide (12.1% in glycolide mol.)

TABLE 8: Effect of Molecular Weight (iv) and composition of the copolymer on the glass transition temperature (^{o}C) of the Copolymer

Composition	iv (dl/g)				
	0.184	0.236	0.5	0.640	0.805
90:10[a]	-	37	49	-	52
70:30	37	-	48	46	-
50:50	-	-	41	-	-

[a] Initial lactide:glycolide w/w ratio.

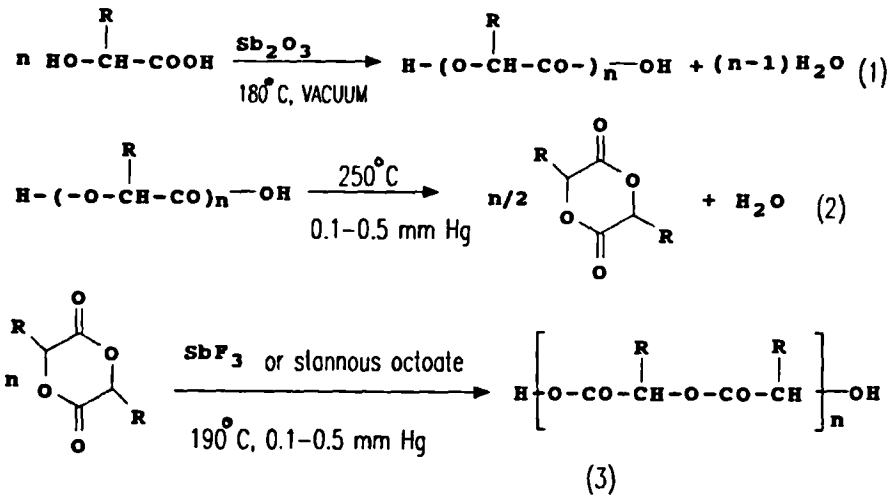


Fig.7 Synthesis of poly(lactide-co-glycolide) polymers (R is H for glycolide and CH3 for lactide).

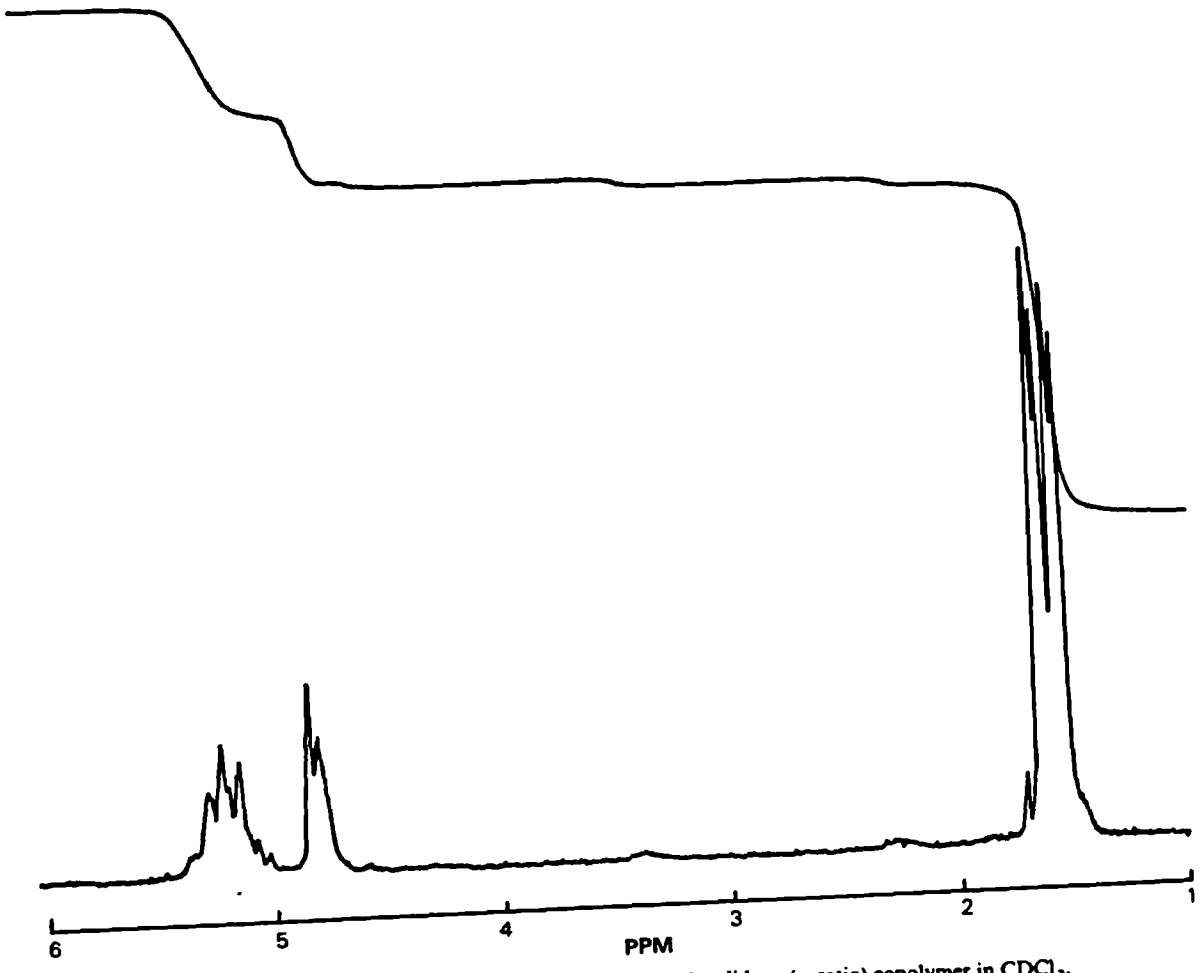


Fig.8 ^{1}H-NMR spectrum of an 80 : 20 (initial lactide : glycolide w/w ratio) copolymer in $CDCl_3$.

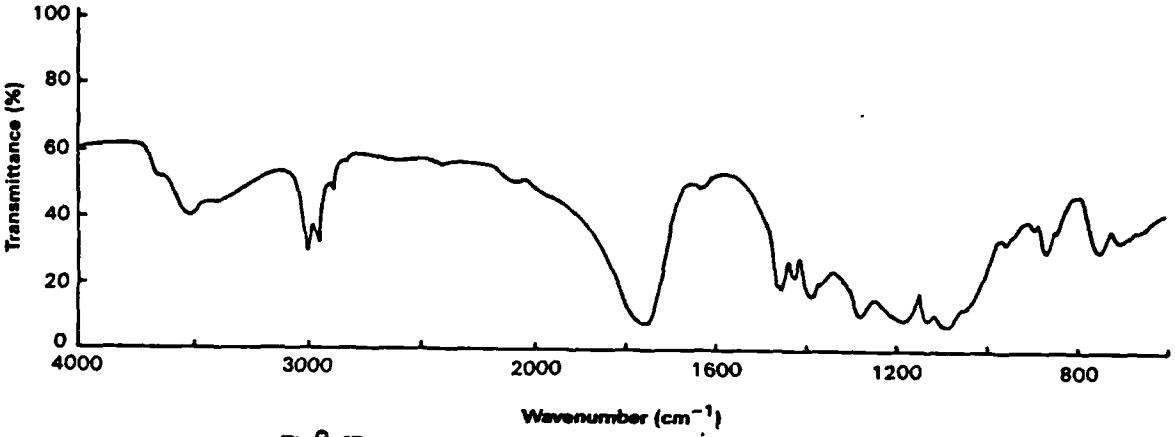


Fig.9 IR spectrum of a 77 : 23 poly(lactide-co-glycolide) copolymer.

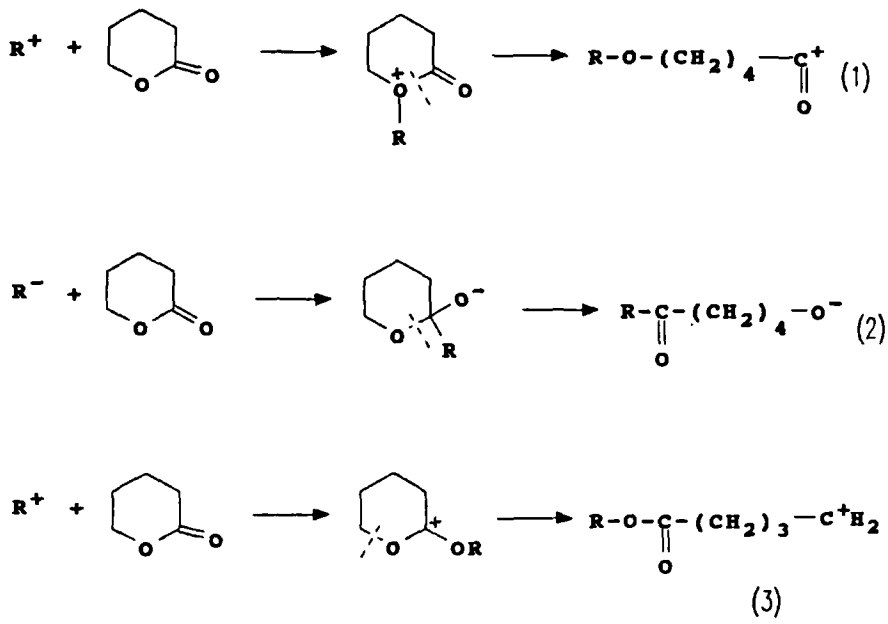


Fig.10 Mechanism of akyl (reactions 1 and 2) and alkyl (reaction 3) cleavage of lactones by cationic (R^+) or anionic (R^-) catalysts.

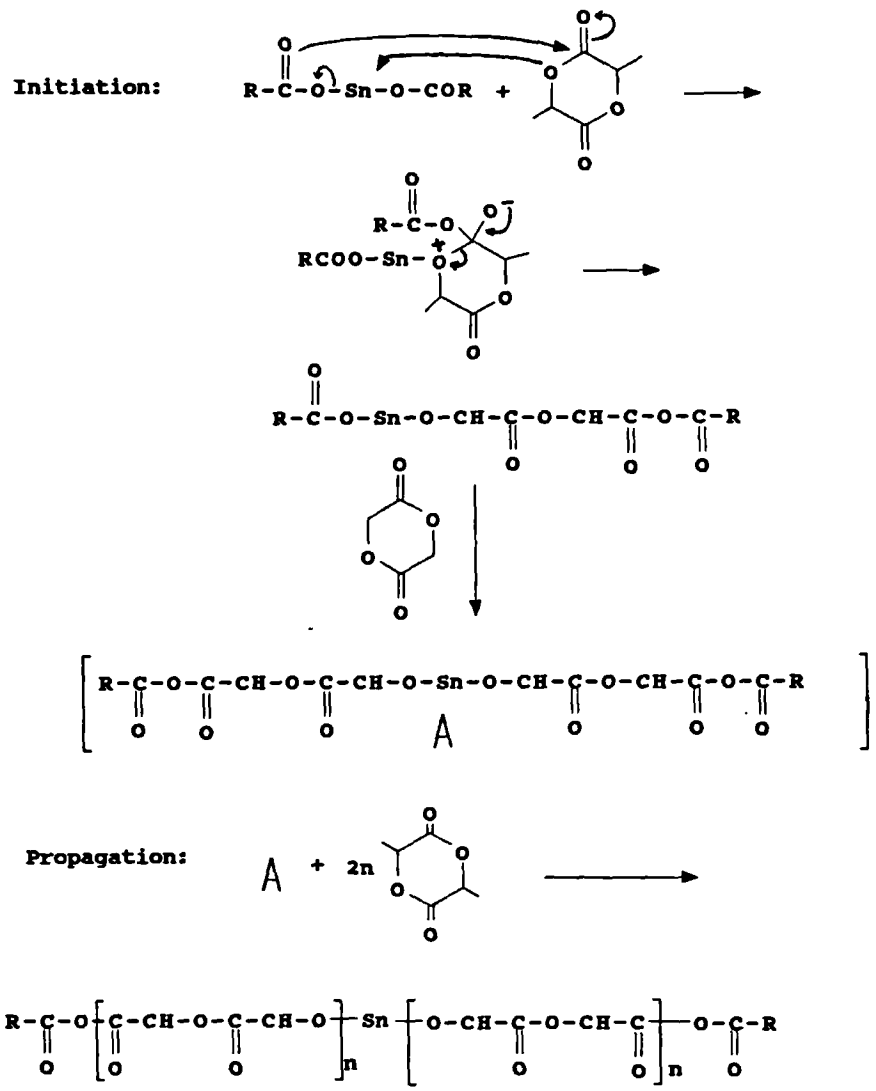


Fig.11 Co-ordinate polymerization mechanism of lactide/glycolide using stannous octoate (RCOOSnOCOR represents stannous octoate).

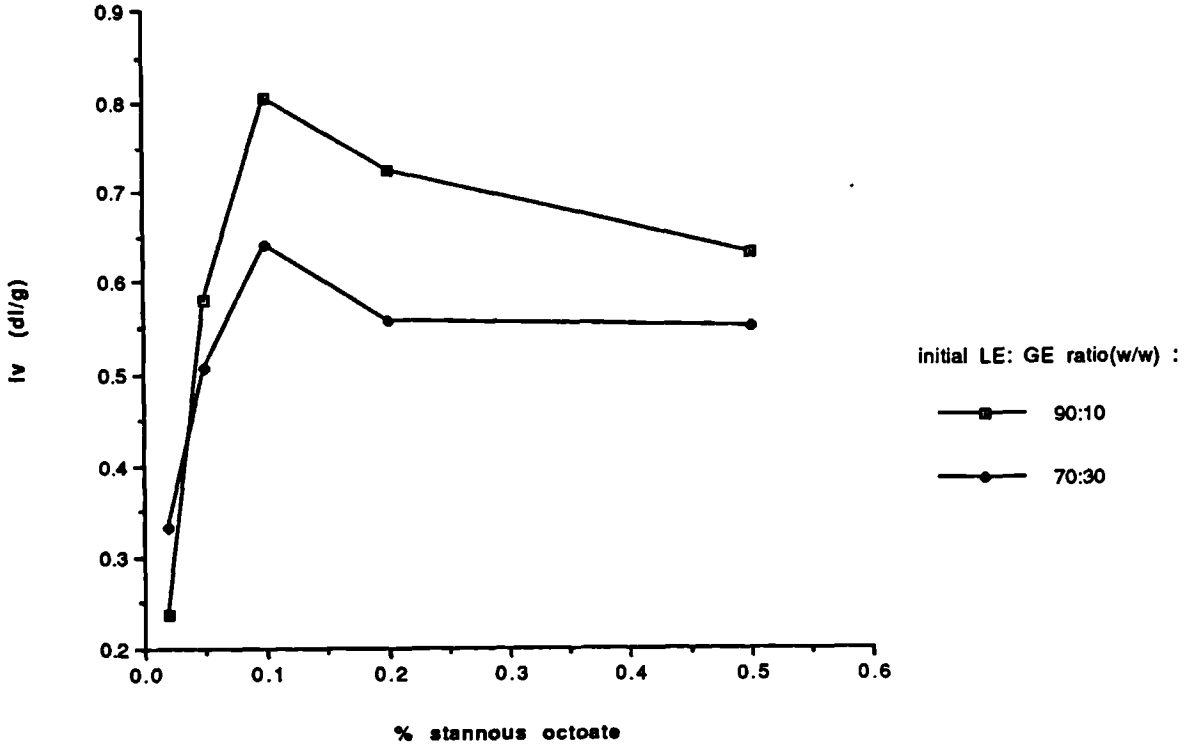


Fig. 12 Effect of catalyst level on polymer mw (polymerization at 190° C for 4 h)

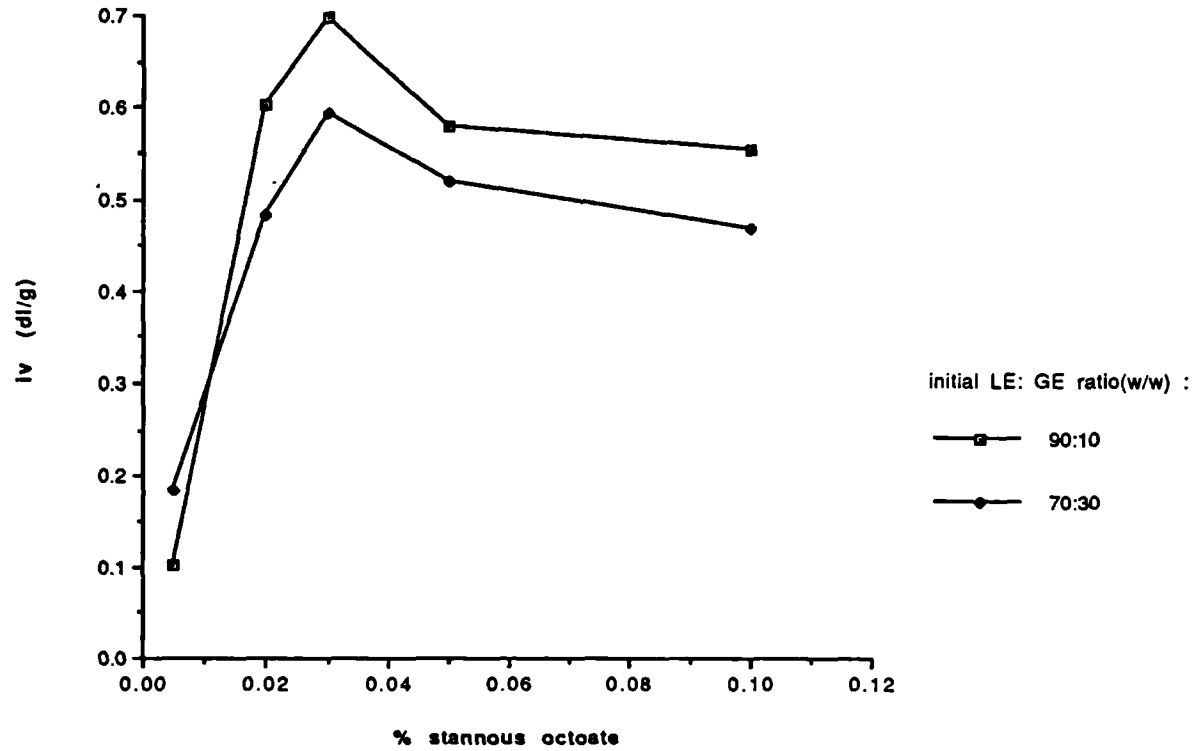


Fig. 13 Effect of catalyst level on polymer mw (polymerization at 130° C for 4 h)

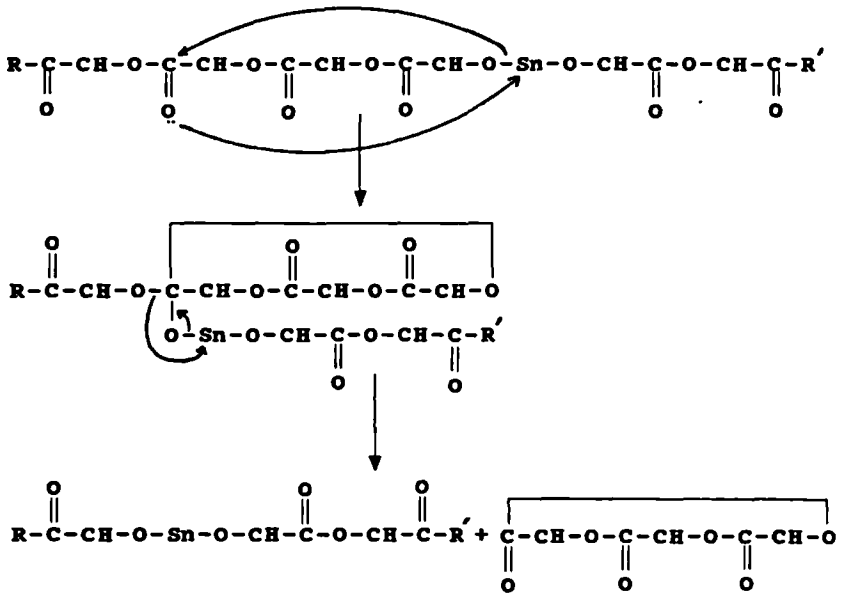


Fig.14 Proposed mechanism of back biting depolymerization reaction (R, R′ polymer chain segments).

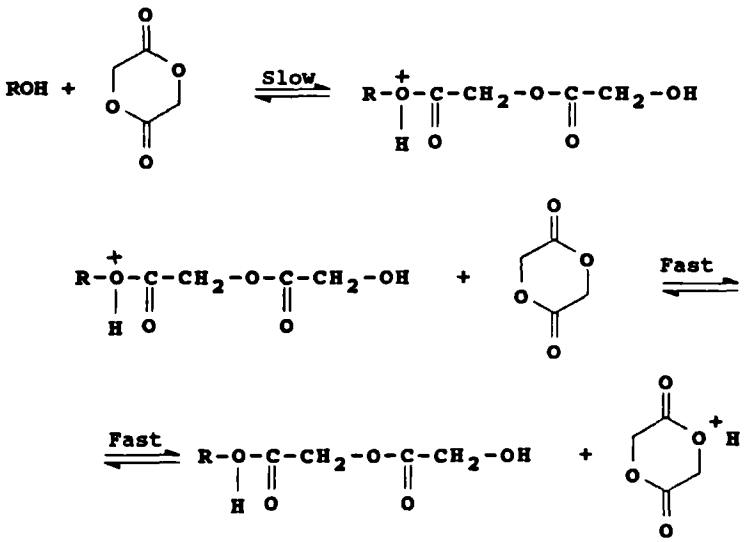


Fig.15 Proposed mechanism for the cationic melt polymerization of glycolide in the presence of alcohol.

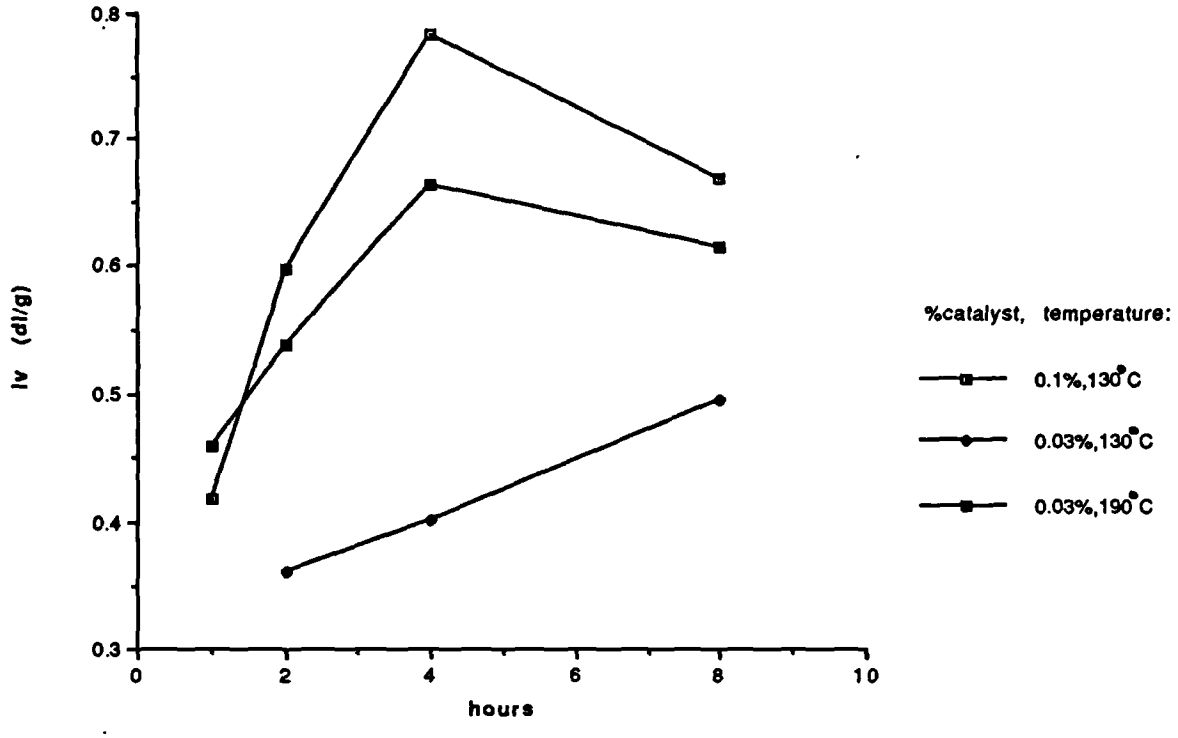


Fig. 16 Effect of reaction time on polymer m w.

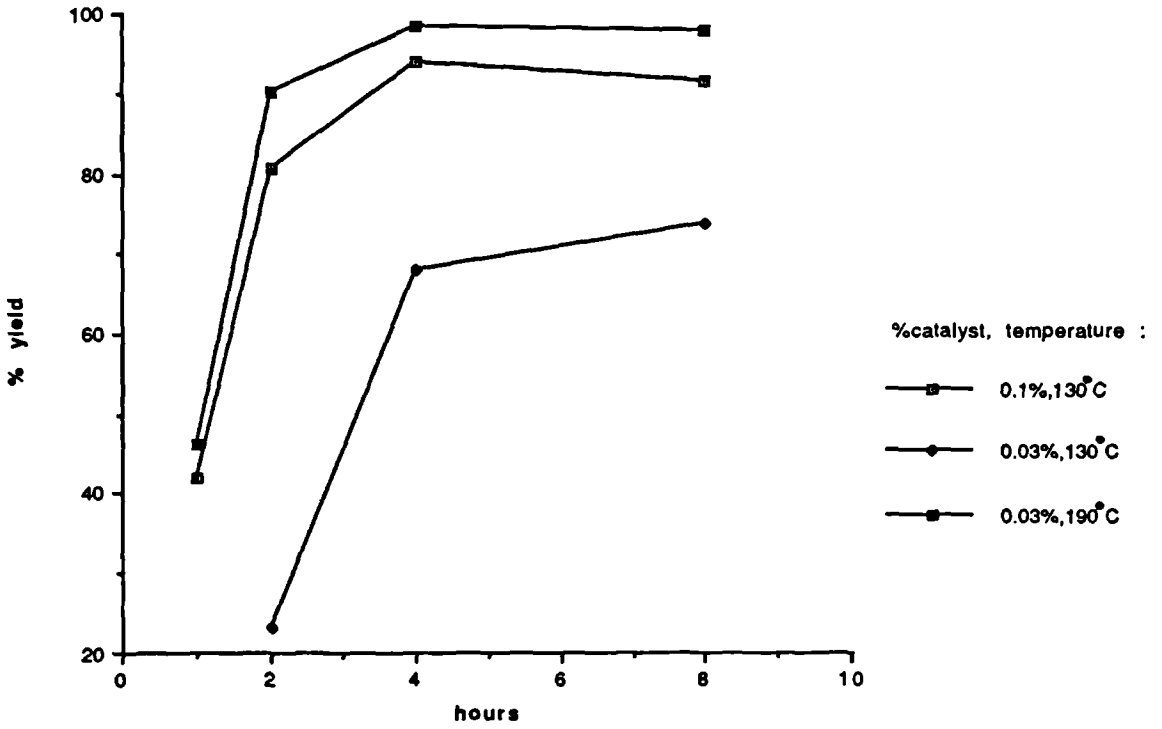


Fig. 17 Effect of reaction time on %yield of polymerization.

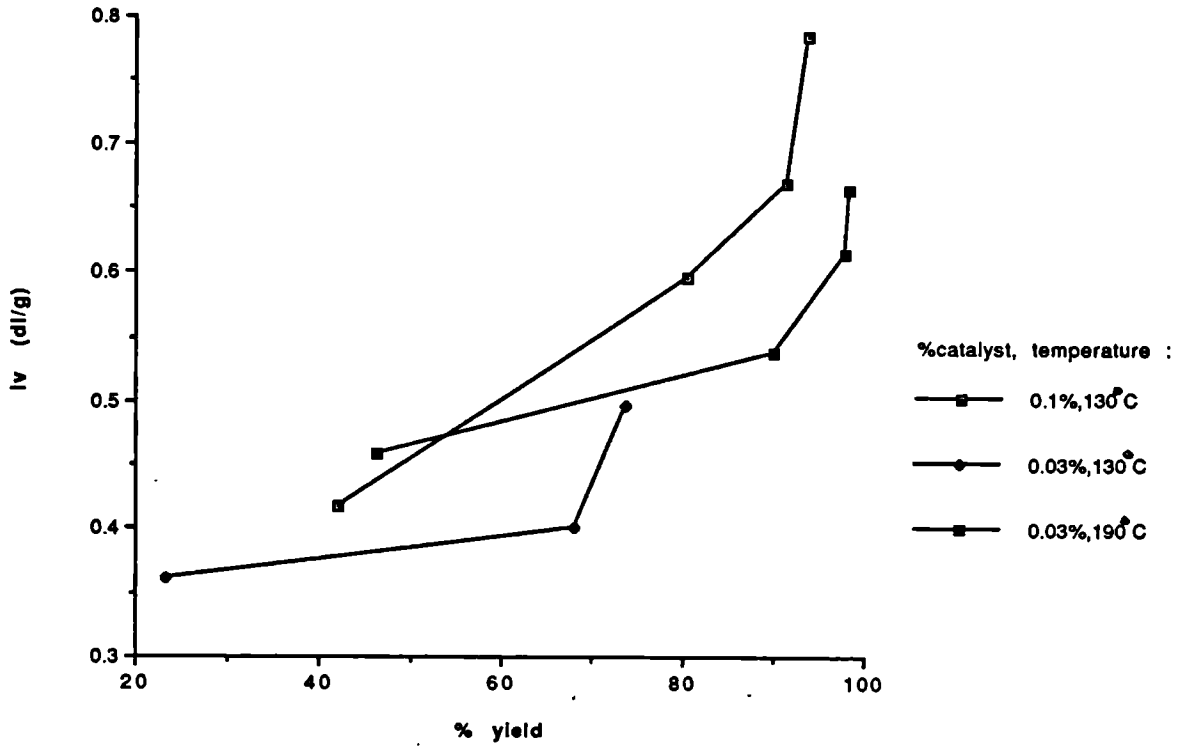


Fig. 18 MW of 90:10 (initial LE:GE w/w ratio) polymers vs %yield of polymerization.

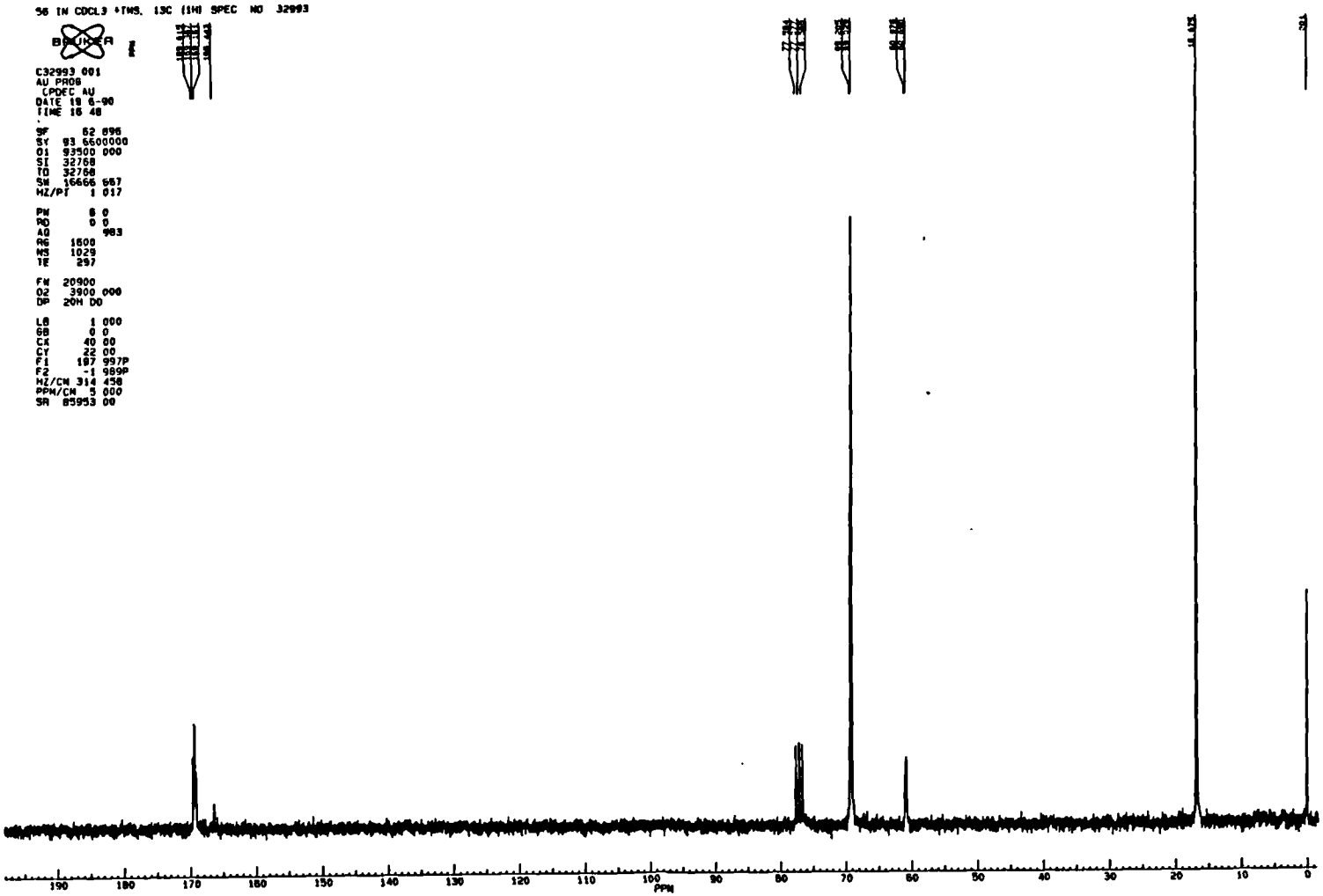


Fig. 19 ^{13}C-NMR spectrum of a 90:10 (initial LE:GE w/w ratio) polymer in $CDCl_3$.

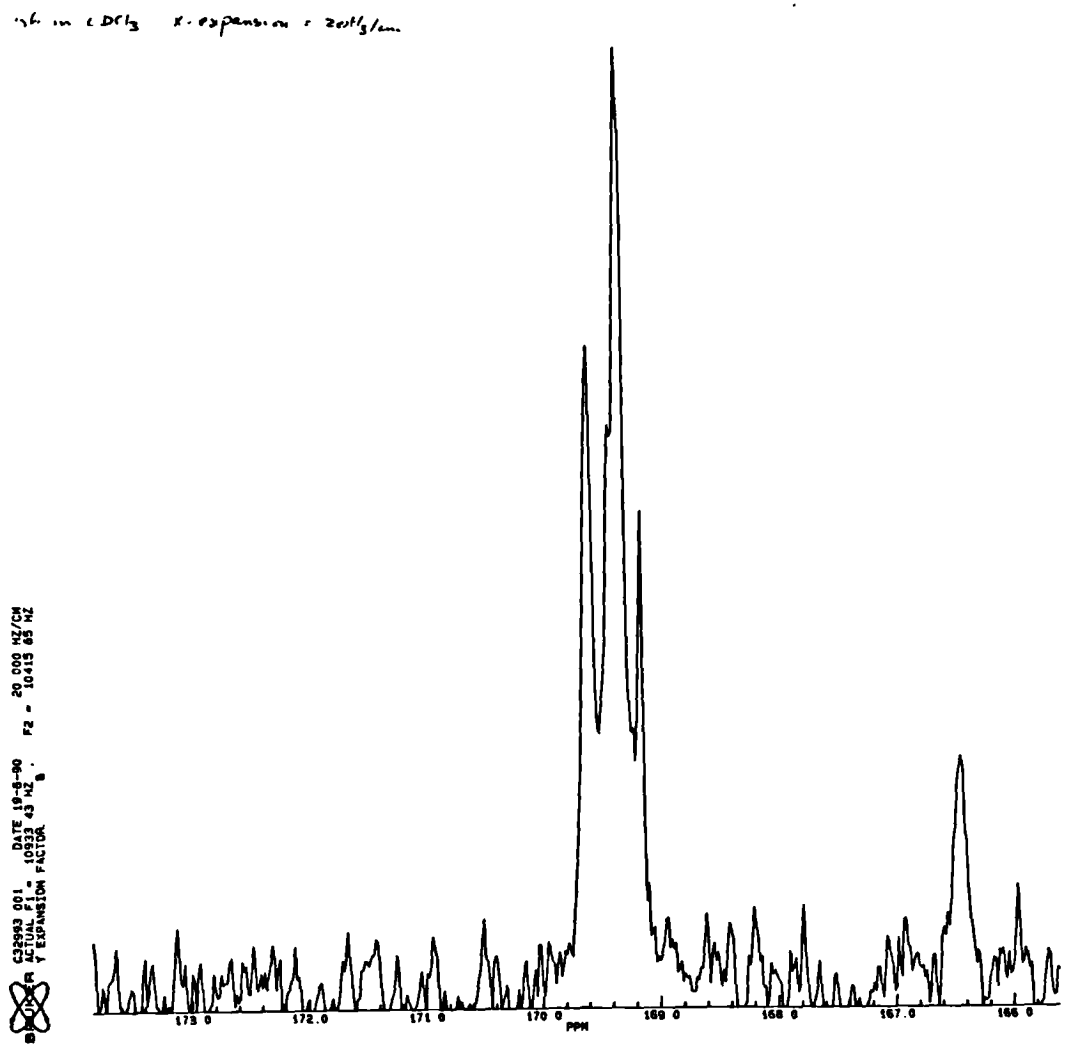


Fig. 20 Expansion of carbonyls carbon resonance of the spectrum shown in Fig.19 .

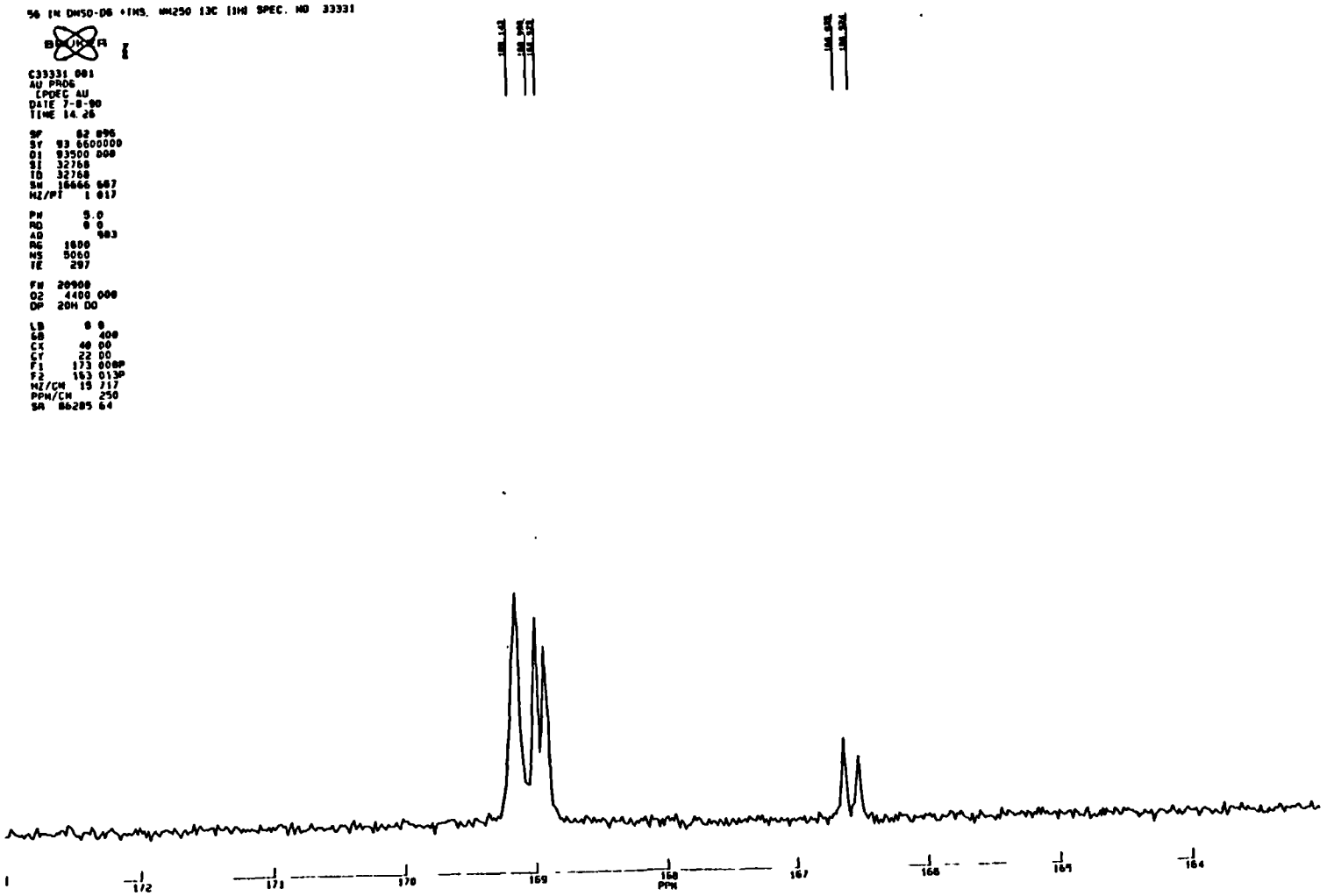


Fig. 21 Carbonyls carbon resonance in DMSO (expanded form) of the same as in Fig. 19 polymer.

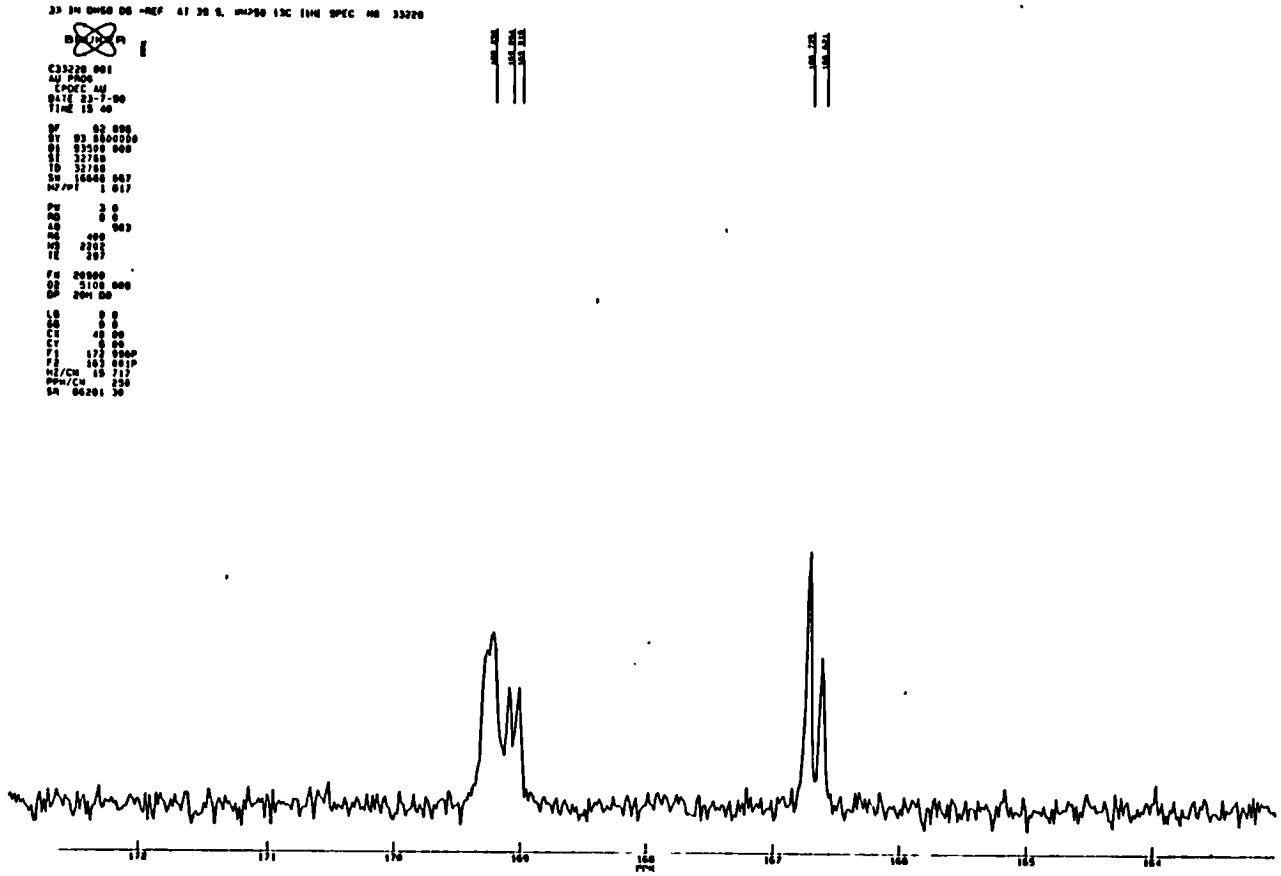


Fig. 22 Carbonyls carbon resonance in DMSO (expanded form) of a 70:30 (initial LE:GE w/w ratio) polymer.

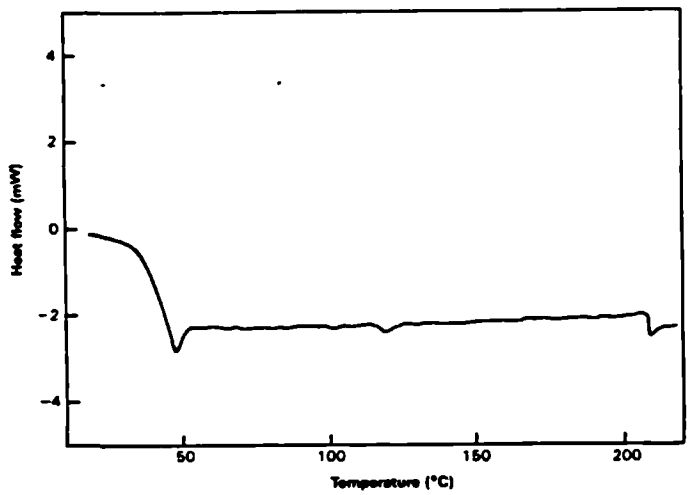


Fig.23 DSC scan of 50:50 poly(lactide-co-glycolide) copolymer (iv = 0.5 dl/g).

3. PREPARATION AND CHARACTERIZATION OF POLY (LACTIDE-CO-GLYCOLIDE) POWDERS

3.1 Introduction

Of all the types of dryer, there are few that accept pumpable fluids as the feed material at the dryer inlet and discharge a dry particulate at the outlet. Of these few, spray drying is unique in being able to produce powders of specific particle size and moisture content irrespective of dryer capacity and product heat sensitivity. Spray drying involves atomization of the feed into a spray and contact between spray and drying medium, usually heated air, resulting in moisture evaporation. The drying of the spray proceeds until the desired moisture content in the dried particles is obtained, and the product is then recovered from the air (Masters, 1985).

Spray drying finds great utility in the pharmaceutical industry because of the rapidity with which drying is achieved and the unique form of the final product. There are three major uses for the spray drying process: (1) drying of heat sensitive materials, (2) changing the physical form of materials for use in tablet or capsule manufacture, and (3) encapsulation of solid and liquid substances. The final product can be in the form of powders, granules or agglomerates. The spherical particles produced usually flow better than the same product dried by other conventional procedures, because the particles are more uniform in size and shape with less sharp edges. The spherical shape has the least possible surface area, thus minimizing air entrapment between particles. This improvement in flow and reduction in air

entrapment makes spray dried materials suitable for use in the manufacture of tablets and capsules (Rankell and Lieberman, 1976).

In the present work poly(lactide-co-glycolide) powders were produced by spray drying chloroform solutions of the polymers. The *in vitro* degradation, hydrophobicity, and compaction behaviour of these powders, which would affect drug release from poly(lactide-co-glycolide) matrix tablets were investigated.

Wettability and water uptake experiments were carried out to assess the hydrophobicity and compaction pressure - compact density (Heckel plots) were used to investigate the compaction characteristics of the poly(lactide-co-glycolide) spray dried powders. The effects of polymer composition and mw on those properties were also considered. Scanning election microscopy (SEM) was employed to examine the morphology of the spray dried particles and the change in appearance of polymer matrices due to degradation.

3.2 Materials and Methods

3.2.1 Materials

Commercial dl-lactide (melting point 125^{o}C) and glycolide (melting point 82^{o}C) both purchased from Boehringer Ingelheim were used to prepare the polymers. The phosphate buffer pH = 7.4 was prepared from 1.19g of potassium

dihydrogen orthophosphate (BDH, GPR), 2.38 g disodium hydrogen orthophosphate (BDH, analar) and 8.0 g of sodium chloride (BDH, GPR) in 1l of distilled water. Chloroform (FSA, analar), methanol (BDH, GPR), dichloromethane (FSA, analar) tetrahydrofuran (FSA, SLR), glacial acetic acid (FSA, SLR), and magnesium stearate (BDH, GPR) were also used.

3.2.2 Methods

3.2.2.1 Synthesis of Larger Polymer Batches

20 g batches of polymers were synthesized as described in paragraph 2.3.2.1.2. These were purified by precipitation from chloroform, using excess methanol, and dried under vacuum at 40^{o}C until of constant weight. The purification of 50:50 (LE:GE%mol) polymers was difficult due to their low solubility. Refluxing for 48 hours in chloroform was used to dissolve the polymers, but some material would not dissolve, probably those polymer molecules containing a high proportion of glycolide blocks, and was removed by filtration. Poly(glycolide) synthesized here could not be purified and characterized due to its insolubility in common organic solvents. It was a brown very hard mass and all attempts to powder it by ball milling failed. Eventually, it was broken down into pieces using the Dartec hydraulic press and used as such in the degradation study.

3.2.2.2 Spray Drying of Polymers

The polymers were dissolved in chloroform to form 2-5% w/v solutions and spray dried using a Buchi mini spray dryer (model 190) to prepare powders. The polymer solutions were sprayed through an atomizer nozzle into a cylindrical (10.5 x 42.5 cm approximately) drying chamber. Atomization was effected by impacting the liquid with high velocity compressor generated air. Drying of the sprayed solutions was effected by a co-current of hot air in the direction of spraying flow.

The process parameters were: inlet temperature, 60^{o}C; outlet temperature, approximately 45^{o}C; aspirator setting, 10; pump setting, 7-10 ml.min^{-1}; spray flow, 400 ml.hour^{-1}. A 0.5 mm nozzle was used throughout the experiments. Material deposited on the walls of the drying chamber was retrieved by dissolving in chloroform and the process repeated. Three spray drying cycles per polymer batch were used. The spray dried polymers were ground to break down the agglomerates using a Moulinette type 320 grinder (Moulinex, France) and sieved to produce powders of known particle-size range. The morphology of the powders was examined using a Phillips EM501B scanning electron microscope (SEM). The spray dried polymers were stored in desiccators over silica gel.

3.2.2.3 Degradation *In Vitro* of Spray Dried Polymers

500 mg of each sample were placed in glass vials containing approximately 25 ml of phosphate buffer, pH = 7.4, and

shaken in a water bath at 37°C. The degradation medium was renewed at 2-week intervals. For sampling, the contents of the vials were poured into sintered glass filters (size 4) and the degradation liquid removed using a water aspirator. The particles were washed with distilled water, filtered and dried in a vacuum oven at 40°C to constant weight. The weight and the inherent viscosity of the dried samples was then measured. Duplicate measurements were carried out over a 12-14 week period. Polymer powders of 420-841μ were used, except with the 50 (0.443) sample for which a higher particle size range, 841-2000μ was used.

3.2.2.4. Compaction Properties of Polymers

The compaction behaviour of spray dried polymer powders was investigated (Heckel, 1961 [a,b]). The powders were compressed using a 10.55 mm diameter flat faced punch and die system (prelubricated with a 1% suspension of magnesium stearate in chloroform) using a Dartec 100 KN M2501 universal testing machine (Dartec, Ltd.). A maximum force of 10 KN was applied at a rate of 0.5 $KN.s^{-1}$ and the force and displacement of the upper punch continuously recorded with a digital storage oscilloscope (Nicolet 3091). The data were analyzed using an Apple IIe computer to produce Heckel plots.

The particle density of powder was measured with a Beckman air comparison pycnometer (Beckman Instruments, model 930). The liquid content (due to residual spray drying solvent or moisture absorbed during storage) of the powders, which

might affect their compaction behaviour, was also determined before the compaction experiments using a Sartorius infrared dryer (Model YDUOIL, Germany). The liquid content of powders was low ranging from 0.2 to 0.6% w/w.

3.2.2.5 Wettability of Polymers

Contact angle measurements were conducted to assess the wettability of spray dried polymer powders. The contact angles were determined by applying the h-ϵ method (Lerk *et al.*, 1976).

The powders (63-150μ) were compressed in a 20 mm diameter flat-faced punch and die set using a RIIC (England) hydraulic press. A load of 1 ton was applied. The dimensions and weight of each disc were measured allowing the calculation of its porosity (ϵ). The disc was placed on a platform which could be adjusted to ensure the disc surface was horizontal. Deionized distilled water was applied to the disc surface via an Agla microsyringe and readings of the drop height were taken with a cathetometer (Graticules Ltd., England) until additional drops caused no increase in height. The contact angle was calculated from the formula (Lerk *et al.*, 1976):

$$\cos\theta = 1 - \sqrt{\frac{2Bh^2}{3(1-\epsilon)}} \qquad \text{Equation 12}$$

where h is the height of the drop and B = $\rho_L.g/2\gamma_{LV}$ where ρ_L is the density of water (1.0 kgl^{-1}, g is the acceleration due to gravity (9.81 ms^{-2}) and γ_{LV} is the water-vapour interfacial tension (0.072 Nm^{-1}). All measurements were carried out at least in duplicate.

3.2.2.6 Water Uptake by Polymers

Tablets were prepared by compressing spray dried polymer powders (63-150μ) in a 10.55 mm diameter flat punch and die system using the Dartec hydraulic press. A 10 KN force was applied at a rate of 1 $KN.s^{-1}$ with a dwell time of 15s.
The tablets, after measuring their dimensions and weights, were placed in glass vials containing phosphate buffer, pH = 7.4, and shaken in a water bath at 37^oC. The weight change of the tablets, with time, was recorded over a 25 day period. The dimensions of the tablets at the end of this period were also measured. SEM photographs before and after water uptake were taken using a Phillips EM 501B SEM.

3.3 Results and Discussion

3.3.1 Synthesis of larger Polymer Batches for Spray Drying

Polymers having compositions ranging from 100% lactide to 100% glycolide were synthesized by polymerizing the monomer mixtures shown in Table 9. Examination of the values in Table 9 show that the proportion of lactide units in the resulting polymer is smaller than that in the initial polymerization mixture, probably because of the greater

reactivity of glycolide during polymerization. The mw of the samples synthesized was regulated by modifying the polymerization conditions according to the results obtained in the study of poly(lactide-co-glycolide) synthesis (Chapter 2). Thus, polymers having iv in the range 0.3-0.4 were synthesized using 0.013-0.016% w/w stannous octoate at 190^{o}C for 5 hours, and polymers having iv in the range of 0.7-0.9 were made using 0.028-0.032% catalyst under the same polymerization conditions. Relatively high mw polymers, iv>1, were synthesized using 0.1-0.12% catalyst at 130^{o}C for 5 hours. A small increase in polymerization time from 4 to 5 hours was introduced because during the polymerization of the first batches unreacted monomer was observed after 4 hours polymerization. The mw of polymers produced under the same polymerization conditions appeared to decrease as the glycolide content of the mixture increased (Figs. 12 and 13), indicating that compositions rich in glycolide require more severe polymerization conditions that compositions rich in lactide. Therefore, slightly higher catalyst levels were normally used for the polymerization of monomer mixtures with a high glycolide content. For convenience, the polymers will be referred to in the following discussion by the designation %LE(iv), i.e. an 85(1.278) polymer is a polymer containing 85% mol lactide with an inherent viscosity in chloroform of 1.278.

3.3.2. Spray Drying Characteristics of Poly(lactide-co - glycolide)

Preliminary spray drying experiments were carried out with

a 85(0.719) polymer but it was found that solutions of this polymer in chloroform having concentration higher than 2% w/v could not effectively be atomized, producing polymer threads instead of particles, irrespective of the spray dryer operating conditions. Similar results were obtained using solvents such as methylene chloride, 2:1, 1:1 and 1:2 v/v mixtures of methylene chloride with chloroform, tetrahydrofuran and glacial acetic acid. A lower mw 85:15 polymer, 85 (0.358), could successfully be "spray-powdered" at concentrations as high as 10% in chloroform. The relative viscosity of a 3% solution of 85 (0.719) polymer (which would give threads) is 5.452, whilst the relative viscosity of a 10% solution of 85 (0.358) is 11.840, i.e. much higher, indicating that the viscosity of the solution was not crucial for the successful spray drying of poly(lactide-co-glycolide) polymers. Bodmeier and Chen (1988) have reported that the successful dispersion of liquid filaments into polymer droplets depended strongly on the type of polymer used and only to a lesser degree on the viscosity of the spray solution.

Even more dilute solutions were required for the effective spray drying of polymers with higher molecular weights, i.e. 1.5% solutions for a 85 (1.278) polymer. It appears that the important factor is the polymer mw but this must be considered in conjunction with the polymer concentration in the sprayed solution. With linear polymers without bulky side groups, such as poly(lactide-co-glycolide), the higher the mw the stronger the intermolecular interactions, i.e. intermolecular attractive forces (Van der Waals

forces), physical entanglement of polymer chains, and this probably accounts for the increased difficulty in breaking up the polymer solution into individual droplets during spray drying as the polymer mw increases. The parallel alignment of the long linear polymer molecules in the liquid filaments leaving the atomizer probably accounts for the production of threads when high mw polymers were sprayed. Diluting the polymer solutions reduces the intermolecular interactions, by increasing the separation of the polymer chains and by allowing a more effective solvating action from the solvent which probably explains the successful "spray-powdering" of high mw polymers using dilute solutions. The spray dried material was deposited in the form of aggregates on the walls of the tube connecting the drying chamber with the cyclone and on the walls of the cyclone. Small quantities of individual particles were collected from the receiving vessel at the bottom of the cyclone. The aggregates were broken down into individual particles by grinding.

There was a significant deposition of partially dried material on the drying chamber wall due to the combined effects of the polymer's nature and the characteristics of the spray dryer used. The high velocity air required to break up the polymer solution into spray droplets projects the spray forward and down the drying chamber at high velocities. Since the drying chamber is small there is not sufficient time for the droplets, especially the coarser ones, to acquire a dry surface, resulting in the deposition of damp particles on the wall. A layer of

sticky material is gradually developed, because of the tacky nature of poly(lactide-co-glycolide) polymers at the drying temperature. Furthermore, the atomizing air that surrounds the spray droplets on leaving the nozzle prevents intimate contact between the hot drying air and the spray resulting in lower evaporation rates, which also contribute to the deposition of semi-wet polymer on the drying chamber wall.

Nevertheless, these deposits could be retrieved and resprayed. The yield after recycling the deposits twice was in the range of 70-80%. The remainder of the material was lost mainly through the discharge of fine particles with the exhaust.

The texture of the spray dried polymer particles was investigated using SEM. The particles, irrespective of their size, appeared to be porous, almost spherical agglomerates of tiny spheres. The agglomerates probably formed through droplets coalescing in the proximity of the atomizer and drying in this state, or alternatively through partially dried droplets adhering to each other in the lower regions of the drying chamber, due to their sticky surfaces. The particle surface was porous and rough but without sharp edges (Fig. 24). Pictures of the interior of the particles showed that the interior had a similar texture to the surface consisting of a large number of very small spheres attached to each other or fused together to form a porous irregular structure (Figs. 25 and 26).

3.3.3 Degradation of Spray dried poly(lactide-co-glycolide) Polymers

Both mass loss and molecular weight reduction, as expressed by the reduction in the inherent viscosity of polymer solutions in chloroform, of a series of poly(lactide-co-glycolide) polymers during incubation in phosphate buffer pH 7.4, 37^{o}C was followed for a 12-week period.

Curves of the percent inherent viscosity (iv) remaining with time for polymers of relatively low molecular weight, initial iv 0.3-0.4, are shown in Fig. 27. An increase in glycolide content of the polymer caused an increase in molecular weight reduction rate, indicating that the hydrolysis of ester bonds proceeded at a higher rate as the glycolide content increased. This can be attributed to the greater susceptibility of the glycolate ester linkage to hydrolysis, as well as to the decrease in the glass transition temperature of the polymers as their glycolide content increases (Table 8). The glycolate ester linkage has a greater susceptibility to hydrolysis than the lactate ester linkage because the lactate ester linkage is subject to steric hindrance, due to the presence of the methyl side group. Glass transition temperature is a measure of the flexibility of the polymer chains and lower Tg values indicate higher chain flexibility and the increased ease with which the transition state for ester linkage hydrolysis may be achieved. Also, the closer the temperature of the incubation medium to Tg, the higher the permeability of the polymer to water and, therefore, an increase in glycolide content could increase the water

penetration rate into the polymer matrix resulting in faster polymer hydrolysis.

The mass loss with time curves for polymers with initial inherent viscosities of 0.3-0.4 are shown in Fig. 28. An increase in the glycolide content of the polymer caused a significant increase in the rate of polymer mass loss. Thus, only 4.5% of the initial weight of a 50:50 (LE:GE% mol) polymer remained after 12 weeks of incubation as compared to approximately 79% of the initial weight of a 100:0 (LE:GE %mol) polymer after the same period. Mass loss occurs when oligomers small enough to dissolve and diffuse out from the matrix have been produced as a result of chain scission. The observed increase in mass loss rate when the glycolide content of the polymer increased is attributable to an increase in the rate of polymer hydrolysis as the glycolide content increases.

Molecular weight reduction with time data could not be obtained for the insoluble poly(glycolide). The mass degradation data for this polymer are shown in Fig. 28. The absence of hydrophobic methyl side groups in poly(glycolide) molecules makes poly(glycolide) the most hydrophillic member in the poly(lactide-co-glycolide) family. However, mass loss from the poly(glycolide) synthesized here proceeded at a rate lower than that anticipated from its hydrophilicity. In fact, only poly(dl-lactide) exhibited a lower mass loss rate than poly(glycolide). Also, a lag period of approximately 2

weeks was apparent in the mass degradation profile of poly(glycolide) (Fig. 28).

Poly(glycolide) has been shown to be a crystalline material (Gilding and Reed, 1979), whilst the remaining polymers synthesized in this work have been found to be amorphous (paragraph 2.4.7). Crystallinity decreases the water penetration rate into the polymer matrix because crystalline regions are more densely packed than amorphous. Chu (1985) reported that the amorphous regions of poly(glycolide) and poly(lactide-co-glycolide) sutures were almost completely degraded *in vitro*, before any degradation in the crystalline regions took place. Also, chain flexibility is reduced in crystalline regions resulting in a decrease in the ease with which the transition state for hydrolysis of the ester bond may be achieved. Therefore, crystalline polyesters would degrade at a lower rate than the amorphous counterparts and this probably explains the relatively low mass loss rate and the presence of the 2-week lag period observed with the crystalline poly(glycolide) (Fig. 28).

The effect of polymer composition has also been investigated using higher molecular weight polymers, i.e. polymers having an initial iv~0.9. An increase in the glycolide content of the polymer caused a decrease in both the chain scission rate and mass loss rate (Fig. 29). Only 9.5% of the initial weight of the 85 (0.901) polymer dissolved over a 12-week period as compared with approximately 62% of the 75 (0.848) polymer during the same

period. An important difference from the low molecular weight polymers was that the mass degradation curves of the high mw polymers exhibited a clear and significant period during which very little mass loss occurred from the polymer, i.e. a lag period (Figs. 28 and 29).

Lag periods prior to weight loss have also been observed with high molecular weight poly(lactide) polymers (Pitt *et al.*, 1981_b, Ogawa *et al.*, 1988_c) and are associated with the time required for the formation of soluble chain fragments during polymer degradation. The lag period appears to decrease with an increase in the glycolide content of the polymer, probably because increasing the glycolide content results in a higher hydrolysis rate. Chain fragments rich in glycolic acid units would be more hydrophillic than chain fragments rich in lactic acid units, therefore, an increase in the glycolide content of the polymer could decrease the extent to which chain fragments have to be reduced before becoming soluble, thus decreasing the lag period.

The degradation data for 50:50 (LE:GE %mol) polymers having different molecular weights are shown in Figs. 30 and 31. All polymers hydrolyzed very rapidly and the molecular weight of many of them was reduced to less than half its original value over a 2-week period. The mw reduction rate appeared to increase slightly as the mw of the polymer decreased (Fig. 30). Thus, the mw degradation half life, $t_{(0.5iv)}$ determined from the iv versus time plots, increased from 1.6 to 2.1 weeks when the iv of the polymer increased

from 0.307 to 0.728. An increase in polymer mw caused a reduction in the density (mol per unit mass of polymer) of hydrophillic chain end groups and resulted in a more hydrophobic polymer, which absorbs water at a lower rate and swells less (paragraph 3.3.6). The glass transition temperature increases with an increase in polymer mw (Table 8), increasing the difficulty with which the transition state for ester bond hydrolysis could be achieved. These factors probably explain the observed decrease in the rate of polymer hydrolysis with an increase in polymer mw (Fig. 30).

Rapid hydrolysis resulted in a rapid mass loss from the 50:50 (LE:GE %mol) polymers (Fig. 31). The rate of mass loss fell with an increase in polymer mw due to the decreased hydrolysis rate as the polymer mw increased. Thus, the mass degradation half life $t_{(0.5M)}$ determined from the mass versus time plots, increased from 3.2 to 6 weeks when the inherent viscosity of the polymer increased from 0.307 to 0.728 (Table 10). The relationship between mass degradation half-life and polymer inherent viscosity was found to be linear (Fig. 32).

An increase in the particle size of the polymer powder, sample 50(0.443) (Figs. (30) and (31) caused a significant decrease in both the mw reduction rate and mass loss rate. The mass degradation curve for the 50(0.443) polymer was almost identical with that of the higher mw polymer, 50(0.643) and the mass degradation half-lives for those polymers were essentially identical, i.e. 5.2 weeks for the

latter and 5.3 weeks for the former (Table 10). The 50 (0.443) sample exhibited the lowest overall chain scission rate amongst the 50:50 (LE:GE% mol) polymers investigated, having an iv reduction half-life of 3.1 weeks, whereas polymers of considerably higher mw, such as 50 (0.728) and 50 (0.643), had iv reduction half-lives of approximately 2 weeks (Table 10).

The increase in the particle size of the polymer powder altered the shape of the iv versus time curve, which became very similar to the mass versus time curve. Thus, the iv versus time curve for the 50 (0.443) sample was the only such curve to have a lag period. After that period, which appeared to last approximately 2 weeks, the hydrolysis rate abruptly increased to become comparable to that of the other 50:50 polymers as indicated from the slopes of the middle portions of the iv versus time plots (Fig. 30). The decreased specific surface area of the sample would cause a decrease in the contribution of surface reactions to the overall hydrolysis and a possible delay in the saturation of the matrix with water. Consequently, there would be a delay in the establishment of the polymer's bulk "equilibrium" hydrolysis rate. This may explain the initial decrease in the hydrolysis rate observed when the particle size of the sample increased. Once the particles have been saturated an "equilibrium" hydrolysis rate is established which depends on the chemical structure of the polymer rather than on the physical form of the polymer matrix. Under these circumstances a sharp increase in the rate of hydrolysis is observed (Fig. 30). The reduced

initial hydrolysis rate as well as the increased difficulty and time required for the removal of soluble chain fragments from the larger particles probably accounts for the decrease in mass loss rate observed with the increase in particle size of the polymer powder (Fig. 31).

Pitt *et al.* (1980) found that the chain scission rate was the same for films and cylinders of poly(ϵ-caprolactone), despite a large surface-to-volume difference, and they suggested that the hydrolysis occurs in the bulk of the material. The results obtained here indicate that when the polymer is in powder form the contribution of surface reactions becomes significant, and that the degradation rate increases with an increase in the specific surface area of the polymer.

The complete mass degradation curves appeared to have sigmoidal shape consisting of three distinctive regions: an initial lag period, an apparent steady-state hydrolysis region and finally a region where the mass loss rate diminishes as the polymer mass is exhausted and the curve levels off (Figs. 28 and 30). In the apparent steady-state region, between approximately 20 and 80% mass loss, the mass loss rate may be considered as constant, implying that the rate of soluble degradation product formation becomes almost constant once sufficient chain scission has taken place to initiate mass loss from the polymer. This may be considered a reasonable possibility for chain scission has been reported to be a random process (Pitt *et al.*, $1981_{a,b}$. Sigmoidal pH versus time curves, with an almost linear

middle region, were previously obtained with poly(glycolide) fibres in water. The decrease in the pH of the solution was attributed to the liberation of glycolic acid resulting from polymer degradation (Chu, 1985).

The effects of polymer molecular weight on poly(lactide-co-glycolide) degradation were also investigated using 85:15 (LE:GE %mol) polymers which degrade at a lower rate than the 50:50 polymers. Three 85:15 polymers were examined having 1.160, 0.901, and 0.423 initial inherent viscosity values. The chain scission rate decreased with an increase in the mw of the polymer (Fig. 33), as with the 50:50 polymers (Fig. 30), but the effect was much more pronounced, due probably to the lower hydrolysis rates of the 85:15 polymers. This indicates that as the glycolide content of the polymer increases the influence of molecular weight on the rate of polymer hydrolysis decreases.

The dependence of hydrolysis rate on polymer molecular weight as found in this study (Figs. 30 and 33) implies that the widespread practice of regarding poly(lactide-co-glycolide) hydrolysis as occurring at a rate independent of the mw of the polymers (Pitt *et al.*, 1981_b, Visscher *et al.*, 1985) and thus assigning degradation rates to poly(lactide-co-glycolide) compositions rather than to individual polymers (Miller *et al.*, 1977, Reed and Gilding, 1981) is inaccurate.

The rate of mass loss from the 85:15 polymers was also affected by the polymer molecular weight. Thus, an

increase in the inherent viscosity from 0.423 to 1.160 reduced the polymer mass degraded over a 12-week period from ~42% to ~3.5%. However, there was no significant difference in the percent mass loss between the 85 (1.160) and the 85 (0.901) polymers over the same period. The lag period prior to mass loss appeared to be a function of the polymer molecular weight (Fig. 34).

Schindler *et al.* (1977) arbitrarily defined lag period as the time required for 5% loss in the weight of the polymer to occur. This definition appears to lack physical significance because it does not take into consideration the relationship between the lag period and the mechanism of polymer degradation. Lag period would be better defined as the time required for an apparent steady-state mass degradation to be established and consequently correspond to the time of the first inflection in the percent polymer mass remaining versus time plot. The lag period could be determined using the mass degradation plots, provided the inflection in the plot is sufficiently sharp. Alternatively, the lag period can be estimated by fitting the data of the steady-state region of the polymer mass versus time plot to zero order rate equations of the general structure:

$$\frac{100M}{M_o} = \alpha - K_{m,o}t \qquad \text{Equation 13}$$

Where M_o and M are the polymer mass at time zero and t respectively, α is the intercept and $K_{m,o}$ the slope of the least square straight line, corresponding to the steady-state mass loss rate. The lag period can be calculated by substituting 100 for 100 M/M_o in equation 15 and solving it with respect to the time:

$$t_{lag} = \frac{\alpha - 100}{K_{M,o}} \qquad \text{Equation 14}$$

This method, unlike the method proposed by Schindler *et al.* (1977), is based on the degradation mechanism and produces lag period values using the actual degradation data of the individual polymer. It can prove particularly useful when the lag period cannot be determined directly from the mass degradation plot, i.e. when the time of steady-state mass loss commencement is not clear, such as in the case of polymers having low molecular weight or high glycolide content (Figs. 28 and 31).

The lag period for the 85:15 polymers could not be determined with the above method because those polymers, especially those having high molecular weight, underwent little mass loss during the 12-week study period. Nevertheless, the lag period appeared to increase with an increase in polymer mw because the high mw 85(1.160) polymer underwent neither significant (~3.5%) nor consistent mass loss during the 12-week period, whilst the low mw 85(0.423) polymer lost approximately 42% of its original weight during the same period (Fig. 34). If the

method of Schindler *et al.* (1977) was applied the lag period values for the 85(1.160), 85(0.301), and 85(0.423) polymers would be ≥ 12 weeks, 6 weeks, and 2 weeks respectively, i.e. the lag period is significantly shortened as the polymer molecular wight falls. The increase in the lag period with the polymer molecular weight has also been observed with poly(lactide) polymers (Pitt *et al.*, 1981[a], Ogawa *et al.*, 1988[c]), and can be attributed to the increased time required for a polymer chain to be reduced to small soluble oligomers during degradation as the polymer molecular weight increases.

The lag period values for all the polymers for which sufficient data points in the steady-state region of the mass degradation curve were available were estimated using equations 13 and 14. The results obtained confirmed that increasing the molecular weight, or the lactide content, of poly(lactide-co-glycolide) polymers produced a longer lag period. Mass loss during the lag period was, in all cases, less than 10%, and did not appear to correlate with the properties of the polymers (Table 11).

The 85:15 (0.423) polymer exhibited lower degradation rate than the 75:25 (0.848) polymer despite its molecular weight being less than half the molecular weight of the (0.848) polymer (Figs. 28 and 29). The degradation rate of poly(lactide-co-glycolide) polymers appears to be more sensitive to changes in polymer composition than to changes in polymer molecular weight. This was further substantiated when the effects of composition and molecular

weight on degradation rate were quantitatively compared. The mass degradation half lives, $t_{(0.5m)}$ of polymers with approximately the same molecular weight (iv~0.3-0.4) but with different composition, i.e. the copolymers in Fig. 28, were plotted against the percent change in lactide content of those polymers, assigning the value zero to the polymer with the lowest lactide content. Thus, the 50(0.343) polymer was assigned the value 0%, so that the 75(0.307) polymer corresponded to a 70% change in lactide content. The slope of the least square - line for the $t_{(0.5M)}$ versus % increase in the lactide content was 0.129 (Fig. 35). The $t_{(0.5M)}$ value for the 85(0.923) polymer was 13.6 weeks as determined by extrapolating the 6 to 12 weeks portion of its mass degradation curve to the 50% mass loss value. This appears to be a reasonable approximation because the actual plot reached 42% mass loss, i.e. very close to 50% value, and because the middle regions of the mass loss curves could be considered to be linear (Fig. 28). Following the previous procedure the $t_{(0.5M)}$ values obtained with 50:50 (LE:GE %mol) polymers having different molecular weights (Fig. 31) were plotted against the percent change in the mw. The slope of the least square line for this data was 0.016 (Fig.36), i.e. much lower than the slope of $t_{(0.5M)}$ versus percent increase in lactide content.

Although hydrolysis of water-soluble esters has been studied widely, the problem as to how OH^- or H_3O^+ attacks the ester bonds of highly polymerized and water-insoluble esters has not yet been solved. It appears that

poly(lactide-co-glycolide) degradation involves random chain scission by hydrolytic cleavage of ester groups (Schindler *et al.*, 1977; Pitt *et al.*, 1981a,b), although an unzipping depolymerization mechanism has also been proposed to operate under certain conditions (Makino *et al.*, 1985). The activation energy values for the degradation of poly(lactide) microcapsules were found to be comparable to those for the hydrolysis of alkyl-acetates (Makino *et al.*, 1985) indicating that degradation of the polymer can be ascribed to hydrolysis. Furthermore, hydrolysis of poly(lactide) and of a 30:70 (LE:GE %mol) copolymer was found to depend on the pH of the incubation medium, accelerating in strongly acidic or strongly alkaline buffered media (Reed and Gilding, 1981; Makino *et al.*, 1986_b) in accordance with the features of acid-base catalysis of ester hydrolysis. Pitt *et al.* (1981_a) proposed that degradation must occur in the bulk of the material because, within limits, the rate of poly(ϵ-caprolactone) chain scission was found to be independent of geometry. Nevertheless, they also reported that the rate of mass degradation *in vivo* was much higher for poly(ϵ-caprolactone) powders than for poly(ϵ-caprolactone) capsules, which was attributed to the greater surface-to-volume ratio of the powder samples. They were unable to decide whether surface reactions involved a biological mechanism or whether it was of the same nature as the degradation in the bulk of the material. The increase in degradation rate *in vivo* of poly(lactide-co-glycolide) powders with an increase in the specific surface area of the sample as found in this study (Figs 30 and 31), implies

that increasing the specific surface area of the sample could alone cause an increase in the degradation rate *in vivo*, although enzymatic involvement would probably supplement the effects of the increased specific surface area.

Poly(lactide-co-glycolide) degradation involves hydrolysis of the polymer chains resulting in a decrease in the polymer molecular weight with time and dissolution of the resulting small chain fragments, which in turn results in time dependent mass loss from the polymer. Hydrolysis of the polymers could be followed by measuring the decrease in their molecular weight with time. However, the measured rate of molecular weight reduction does not necessarily reflects the actual rate of ester bonds cleavage. In some cases the inherent viscosity appeared to level off, or to increase during certain periods of the degradation, which, superficially interpreted, would mean that in those cases the hydrolysis had been discontinued or chains were reconnected causing an increase in polymer molecular weight. A possible explanation for this phenomenon could be that, during those periods, the rate of polymer hydrolysis had become lower than the rate of small chain fragments removal by diffusion into bulk solution and the molecular weight of the residual polymer particle being an overage, increased (Figs. 27, 29, and 30). It would appear, therefore, that the rate of molecular weight reduction would reliably reflect the rate of polymer hydrolysis only before the onset of mass loss from the polymer.

Pitt *et al.* (1981 $_{a,b}$) proposed that the hydrolysis of poly (ϵ-caprolactone) and related polyesters is autocatalyzed by the generated carboxylic acid end groups. Evidence for this was provided when the partial ethoxylation of the initially present carboxylic acid end groups ("end capping") caused a decrease in the rate of poly (ϵ-caprolactone) chain scission in deionized water. It was assumed that the carboxylic acid groups would not be dissociated in the hydrophobic polymer bulk, and that they would function by hydrogen bonding to the ester links (Pitt and Gu, 1987).

Neglecting the contribution of uncatalyzed hydrolysis the rate of chain scission of an aliphatic polyester autocatalyzed by the generated carboxylic acid end groups, would be given by:

$$\frac{d[COOH]}{dt} = K[COOH]\ [ester]\ [H_2O]$$

Equation 15

where K is a rate constant and [COOH], [ester], and [H_2O] are the concentrations of carboxylic acid end groups, ester, and water molecules respectively.

For a small number of chain scissions, the ester as well as the water concentration can be considered constant and equation 15 simplifies to equation 16:

$$\frac{d[COOH]}{dt} = K'[COOH]$$

Equation 16

Integrating eq. 16 leads to :

$$\frac{[COOH]}{[COOH]_o} = e^{k't}$$

Equation 17

and provided that [COOH] = M_n^{-1} equation 17 can be rewritten as:

$$\frac{1}{M_n} = \frac{1}{M_n^o} e^{k't}$$

Equation 18

Substitution of the Mark-Houwink relationship (equation 19) into equation 18 gives equation 20:

$$[n] = K'' M_n^{\alpha}$$

Equation 19

$$[n] = [n]_o \; e^{-\alpha k't}$$

Equation 20

Taking the natural logarithms of both sides in equation 20 results in:

$$\ln[n] = \ln[n]_o - ak't$$

Equation 21

In the derivation of equation 21 it was assumed that the carboxylic acid end groups participate in the transition state of the hydrolysis reaction in their undissociated from. However, the hydrolysis of ester bonds in neutral and alkaline buffered media will more probably generate carboxylic acid end groups in their dissociated form. The pK_a of carboxylic acid end groups in poly(lactide-co-glycolide) polymers may reasonably be assumed to

approximate closely to that of lactoyllactic acid, which has been reported to be ~ 3.0 (Schindler *et al.*, 1977). Application of the Henderson-Hasselbach equation (equation 22) for the dissociation of a weak acid with pK_a = 3.0 shows that the concentration of the dissociated carboxylic acid end groups in an aqueous environment of pH = 7.4, such as the phosphate buffer used in this work, will be more than 25 X 10^3 times greater than the concentration of the undissociated carboxylic acid end groups (equation 25):

$$pH = pka - \log \frac{[COOH]}{[COO^-]}$$

Equation 22

and

$$7.4 = 3.0 - \log \frac{COOH]}{[COO^-]}$$

Equation 23

and

$$\log \frac{[COO^-]}{[COOH]} = 4.4$$

Equation 24

leading to:

$$\frac{[COO^-]}{[COOH]} \sim 25{,}119$$

Equation 25

If dissociation of carboxylic acid end groups is assumed the hydrogen ion concentration will be proportional to the square root of the acid concentration (Pitt *et al.*, 1981a): Where $K_D^{0.5}$ is proportionally constant.

$$RCOOH \rightleftharpoons RCOO^- + H^+$$

Equation 26

$$[H^+] = K_D^{0.5} [RCOOH]^{0.5}$$

Equation 27

The possibility that the generated hydrogen ions catalyze the hydrolysis of ester bonds cannot be ruled out. The hydrolysis rate of poly(ethylene terepthalate) by water vapour at 150-220°C has been found to be proportional to $[COOH]^{1/2}$ (Ravens and Ward, 1961). In this case it can be written:

$$\frac{d[COOH]}{dt} = K_1 [COOH]^{0.5}$$

Equation 28

which is equivalent to

$$\frac{d[COOH]}{[COOH]^{0.5}} = K_1 dt$$

Equation 29

Integration of Equation 29 leads to:

$$2([COOH]^{0.5} - [COOH]_o^{0.5}) = K_1 t$$

Equation 30

and rearrangement gives

$$[COOH]^{0.5} = [COOH]_o^{0.5} + \frac{k_1}{2} t$$

Equation 31

Provided [COOH] = M_n^{-1} equation 31 becomes:

$$(M_n)^{-0.5} = (M_n^o)^{-0.5} + \frac{1}{2}K_1 t$$

Equation 32

Substitution of the Mark-Houwink relationship (equation 19) into equation 32 leads to:

$$[n]^{-0.5/a} = [n]_o^{-0.5/a} + K_2 t$$

Equation 33

where

$$K_2 = \frac{1}{2}K_1 (K'')^{-0.5/a}$$

When the polymer is in powder form the contribution of reactions occurring on the surface of the particles to the overall hydrolysis should be significant. These surface reactions will be controlled by the properties of the incubation liquid which will, exert great influence on the degradation kinetics. In accordance with this Makino *et al.* (1986$_{a,b}$) found that the degradation rate of poly(lactide) microcapsules was significantly affected by the pH and ionic strength of the bulk solution. In buffered neutral to slightly alkaline solutions such as phosphate buffer, pH = 7.4, and the physiological environment the acidic degradation products will be converted into neutral salts. In those media autocatalyzed hydrolysis should be negligible. Chu (1982) observed differed degradation kinetics of poly(glycolide) fibres in acidic than in neutral buffer media and the difference was attributed to the lack of autocatalyzed hydrolysis in the neutral buffer media.

If poly(lactide-co-glycolide) hydrolysis is not autocatalytic chain cleavage will follow the rate law:

$$\frac{d[COOH]}{dt} = K_3[ester]\ [H_2O]$$

Equation 34

Before any noticeable mass loss from the polymer takes place the concentration terms in the right side of equation 34 may be treated as constant and equation simplifies to:

$$\frac{d[COOH]}{dt} = K_4$$

Equation 35

where $K_4 = K_3\ [COOH][H_2O]$

Integration results in:

$[COOH] - [COOH]_0 - K_4t$ Equation 36

and provided that $[COOH] = M_n^{-1}$ equation 36 becomes:

$$(M_n)^{-1} - (M_n^o)^{-1} = K_4t$$

Equation 37

Substitution of the Mark-Houwink relationship (equation 19) into equation 37 leads to:

$$[n]^{-1/a} - [n]_o^{-1/a} = K_5t \quad where \quad K_5 = K_4\,(K'')^{1/a}$$

Eq. 38

Equation 38 is equivalent to the following equation:

$$[n]^{-1/a} = [n]_o^{-1/a} + K_5t$$

Equation 39

Using the Solomon-Ciuta approximate relationship (equation 7, paragraph 1.3.3.2) the inherent viscosity versus time degradation data for the polymers which underwent comparatively little mass loss over the 12 week period were converted to intrinsic viscosity [n] versus time data. For the 75 (0.848) polymer degradation data prior to the fourth week of incubation were used because the polymer suffered significant mass loss after that period (Fig.29). The intrinsic viscosity versus time data so generated were fitted to the kinetics equations 21, 33, and 39 using the values 0.75 and 0.66 as the Mark-Houwink exponent α for poly(lactide) and poly(lactide-co-glycolide) respectively (Schindler and Harper, 1979; Pitt and Gu, 1987). Better correlation coefficients were obtained by fitting the data to equation 39 (Table 12) indicating that the hydrolysis of poly(lactide-co-glycolide) spray dried powders was not autocatalyzed by the generated carboxylic acid end groups. This result justifies the reservations for the degradation mechanism proposed by Pitt *et al.* ($1981_{a,b}$) discussed previously. It would appear that autocatalyzed bulk hydrolysis might be the predominant degradation mechanism for the degradation of comparatively highly hydrophobic poly (ϵ-caprolactone) in acidic or not buffered media, but the degradation of the more hydrophillic poly(lactide-co-glycolide) in neutral buffer media appears to follow non autocatalyzed hydrolysis kinetics.

Examination of the hydrolysis rate constants in Table 12 confirms that the rate of poly(lactide-co-glycolide) hydrolysis is a function of the polymer properties,

increasing with an increase in glycolide content or with a decrease in the molecular weight of the polymer.

3.3.4 Compaction Behaviour of Spray Dried Poly(lactide-co-glycolide) Polymers

Heckel (1961 a,b) considered the compaction of powders to be a first order reaction, the pores being the reactant and densification the product. He proposed the following equation:

$$\ln\left(\frac{1}{1-D}\right) = KP + A$$

Equation 40

where D is the relative density of the compact (apparent density of the tablet divided by the particle density), P is the applied pressure and K, A constants.

Considerable deviations from this expression by the experimental data occur at both low and high pressures, due to particle rearrangement and strain hardening respectively, or as compact density approaches the true density of the powder at high pressures, but over the middle pressure range a straight line relationship between ln(1/1-D) and P exists, so that the constants K and A can be determined from the slope and the intercept respectively of the extrapolated linear region of ln (1/1-D) versus P plots. The reciprocal of constant K is numerically equal to the yield pressure (P_Y) of the material and the higher the value of K the softer and more ductile a powder is. The constant A represents the densification effected by

filling the die and by individual particle movement and rearrangement at low compaction pressures.

A typical Heckel plot for poly(lactide-co-glycolide) spray dried powders is shown in Fig 37. The plot consisted of an initial curved region, during which densification occurred through particle slippage and rearrangement, followed by an essentially linear region during which densification through plastic deformation took place. The P_Y values of the polymers, calculated from the slope of the 2.5 to 3.5 KN part of the Heckel plots (each KN of compaction force in the abscissa of the plot corresponds to 11.44 MPa of compaction pressure), were in the range of 28-33 MPa, indicating a material of high plasticity. The loose and porous texture of the spray dried polymer particles, decreasing the resistance of the powder to deformation, contribute to the low P_Y values observed (Table 13). The P_Y values obtained are in the range of P_Y values reported for other polymeric materials used as pharmaceutical excipients (the P_Y values for poly(vinyl chloride) and poly(ethylene) have been found to be 69.8 and 15.5 MPa respectively, and similar to the P_Y value of maize starch, a common direct tableting excipient, for which P_Y = 40.3 MPa (Roberts and Rowe, 1987).

Heckel plots have been used to elucidate the consolidation mechanisms during the compaction of powders. The form of the Heckel plots obtained with different particle size fractions has been used to differentiate between materials

consolidating by plastic deformation, or fragmentation. Upon compaction, the former produce parallel lines which represent the different densification obtained with different particle size fractions, whilst the latter give coincident straight lines above a certain compaction pressure. However, the type of Heckel plots may vary depending on the experimental compaction technique used and different particle size fractions of the same material may exhibit changes in the predominant consolidation mechanism ranging from brittle to plastic deformation, so that classification of a material using data for a range of particle sizes would appear to be unreliable (Rue and Rees, 1978). A more reliable way to elucidate the consolidation mechanism could be to obtain Heckel plots of a material using different compaction rates (Rue and Rees, 1978). Plastic deformation is time dependent and materials consolidating through plastic deformation should exhibit a significant increase in consolidation with decreasing compaction rates. The P_Y of spray dried poly(lactide-co-glycolide) increased from 28.43 to 48.69 MPa when the compaction rate increased from 0.5. to 1.5 $KN.s^{-1}$ (Table 13), indicating that plastic deformation is the predominant consolidation mechanism.

It can be seen in Fig 37 that even at low compaction pressures a compact of high density results. For example at 5 KN (57.20 MPa) ln (1/1-D) equals 2.5 and consequently n=0.918. This demonstrates the high ductility of the spray dried polymers and implies that, even at low pressures, strong tablets should be produced, because high density

values mean more intimate contact between the particles and strong interparticle bonding.

The characteristics of the polymers, such as composition and molecular weight, did not appear to have any significant effect on the yield pressure of the powders over the range studied (Table 13).

3.3.5 Wettability of Spray Dried Poly(lactide-co-glycolide) Polymers

The contact angle values obtained with polymers of different composition and mw were in the range of 72-78^{o} (Table 14), indicating a moderate polymer hydrophobicity. The positive values of Cosθ (Table 14), imply that water would penetrate into the heterogeneous poly(lactide-co-glycolide) matrix since a positive capillary pressure differential (ΔP) would exist (as shown by equation 41) and this would draw water into the matrix:

$$\Delta P = \gamma \cos \Theta / m$$

Equation 41

where γ is the surface tension of the liquid, θ is the liquid-solid contact angle, and m is the ratio of the cross-sectional area of the capillary to its perimeter (Ganderton and Selkick, 1970).

The polymer mw did not appear to have any effect on poly(lactide-co-glycolide) wettability in contrast to the effect of composition (Table 14). Thus an increase in

glycolide content tended to increase the polymer wettability due to the decreased number of hydrophobic lactic acid methyl side groups in the polymer chain as the glycolide content increased. However, the contact angle values obtained from polymers of different composition, but similar mw, i.e. the polymers in Table 14 having IV ≈ 0.8, were not found to differ significantly (0.05 level of significance) when using the analysis of variance (ANOVA) statistical method (Table 15). ANOVA was carried out using the KWIKSTAT version 2.00 (Texasoft/Mission Technologies, Texas, USA, 1989) statistical software.

3.3.6 Water Uptake from poly(lactide-co-glycolide) Matrices

Water uptake from poly(lactide-co-glycolide) matrices increased steadily with time and no equilibrium was reached because degradation caused a continuous transformation throughout the experiment causing the matrix to become more hydrophillic (Figs. 38 and 39). Chain scission, which starts immediately after the immersion of the polymers in the liquid (paragraph 3.3.3) generates hydrophillic groups (hydroxyl and carboxylic acid end groups), which cause this increase in the matrix hydrophilicity. The oligomers also produced when extensive chain scission has occurred would create an osmotic pressure difference between the interior of the tablet and the surrounding liquid, because the oligomers formed in the interior diffuse out from the matrix at lower rate than those formed at the tablet surface. This would draw water into the matrix, the outer

layers of the tablet functioning as a "semipermeable membrane".

Advanced degradation, after prolonged periods of immersion in an aqueous medium, turns the interior of the matrix into a hydrogel (Fig.5.6) which is capable of absorbing large qualities of water. Thus, the hydrolysis of the polymer causes water to be drawn continuously into the matrix, and the weight of the matrix increases with time, but degradation is proceeding continuously and eventually when mass loss due to this outweighs the gain from water uptake the weight of the matrix begins to fall (Fig. 38).

An increase in glycolide content caused an increase in both the percent water uptake and water uptake rate (Fig. 38). This can be attributed to the increased polymer hydrophilicity and to the decrease in the Tg of the polymer, which will enhance the permeability of the polymer in water and increase the amount of water that can be accommodated by the polymer. A decrease in polymer mw caused an increase in both the percent water uptake and water uptake rate (Fig. 39) because of the increased polymer hydrophilicity and the decreased Tg of the polymer.

The 85(0.308) and 50(0.343) polymers showed similar water uptake profiles, characteristic of their low mw. After the initial burst the water uptake rate assumed a fairly constant lower value for the remainder of the process, only increasing in the final stages (Figs. 38 and 39). The constant water uptake rates, calculated by fitting the data

between the initial burst and the final stages to zero order rate equations, were 1.10 (r = 0.9978) and 1.70 $mg.day^{-1}$ (r = 0.9995) for the 85(0.308) and 50(0.343) polymers respectively. The mechanism responsible for the increase in water uptake during the concluding stages is probably associated with the transformation of the central portion of the 85(0.308) and 50(0.343) tablets into hydrogels, due to advanced polymer hydrolysis (Fig. 56). The water uptake experiments lasted 20 days for the 50 (0.343) and 25 days for the remaining polymers. When the experiment was discontinued the 50(0.343) and 85(0.308) tablets had become highly deformed and softened. They had also filled with water, which would have been squeezed out of the matrices under the lowest pressure. The 50(0.343) polymer, which according to the degradation data obtained here exhibits the highest degradation rate [the mass degradation half-life of this polymer in powder form was found to be approximately 26 days (Table 10)], was the only matrix for which a weight reduction was observed during the 25 days of the water uptake experiment (Fig. 38). After 20 days immersion in, pH = 7.4, the interior of the 50(0.343) tablets had been completely dissolved and after drying tablets with an empty central portion and highly eroded surface layers were obtained (Fig. 40). The big difference in the extent of degradation between the 50(0.343) polymer and the high mw 75(1.134) polymer is clearly demonstrated in Figs. 40 and 41.

High mw polymers did not degrade significantly during the 25 day experimental period and the tablets retained their

initial shape and strength (Fig. 41). The more hydrophobic ones, i.e. the 100(1.178) and the 85(1.278), absorbed water at relatively low rates, 0.082 (r = 0.9920) and 0.147 $mg.day^{-1}$ (r = 0.9846) respectively. These rates were calculated from the slopes of the linear regression lines of the% water uptake versus time data. The 75(1.134) polymer, which is the most hydrophillic of the high mw polymers studied here, showed a "mixed" water uptake profile; the first part resembling the water uptake profile of the high mw polymers, whereas the second that of the low mw polymers (Fig. 38). An abrupt increase in water uptake rate occurred in the middle of the 25 days period, the water uptake rate being 0.483 $mg.day^{-1}$ before the point of inflection on day 13 and 1.109 $mg.day^{-1}$ afterwards, when calculated by fitting the data before and after the point of inflection to the zero order rate equation, r = 0.9651 and r = 0.9979 respectively. These results indicate that the hydrophilicity of the matrix increased after 13 days immersion probably due to polymer hydrolysis occurring during the first 2 weeks. The observed 40% reduction in the iv of a 75(0.848) polymer over the 2 week period would support this contention (Fig. 29).

After the initial burst water uptake rate appears to decrease with time as "saturation" of the matrix approached. The "saturation" involves not only the filling with water of capillaries and pores within the matrix, but also the saturation of the polymer itself, as indicated by the considerable swelling observed during the initial stages of water uptake. Thus, the 100 (1.178), 75 (1.134)

and 50 (0.343) matrices swelled by 12.71, 27.30 and 30.56% respectively after 2 days immersion in buffer, pH = 7.4. The decrease in water uptake rate is more evident with polymers having a relatively low water uptake rate (Figs. 38 and 39). Accordingly, an "equilibrium point" can be defined as that point of the initial water uptake versus time curves where the rate of water uptake becomes minimum. As no significant degradation, or at least no degradation sufficient to bring about an increase in water uptake rate, has occurred until this point the water uptake at "equilibrium point" can be considered to reflect better the inherent hydrophilicity of the original polymer than water uptake values obtained after the initiation of polymer degradation. Furthermore, the data up to "equilibrium point" can be analyzed to elucidate the water uptake kinetics before any significant degradation takes places and to assign a water uptake rate value for each sample.

The water uptake rate became minimum after 5 days for the 100(1.178), 85(1.278), 75(1.134) and 85(0.727) polymers; after 2 days for the 85(0.308) and after 3 days for the 50 (0.343) polymer. The time required for "saturation" appeared to depend on the hydrophilicity of the polymer and on the weight of the matrix (Table 16). These data up to equilibrium were fitted to zero, first and Higuchi kinetics. The regression equations describing Higuchi kinetics had the form:

where M_o, M are the matrix weight at time zero and t respectively, and α, K constants. This equation provided the best fit, as indicated by better correlation

$$(M - M_o)\ 100/M_o = \alpha + kt^{0.5}$$

Equation 42

coefficients, suggesting that the water uptake followed Higuchi kinetics. The slopes of the regression lines resulting from fitting the data to Higuchi's model correspond to the water uptake rate constants. Both the water uptake rate and the percent water uptake at "equilibrium" increased with an increase in glycolide content, or a decrease in the mw of the polymer (Figs. 38 and 39, Table 17).

The swelling (% increase in tablet thickness) of the tablets after 25 days immersion in phosphate buffer, pH = 7.4, increased with an increase in glycolide content, or a decrease in mw of the polymer (Table 18). The increased polymer affinity for water, as hydrophilicity of the polymer increases, accounts for the observed increase in swelling. Unexpectedly, and in contrast to thickness the diameter of all tablets appeared to decrease slightly (1-2%) after 25 days of immersion. This can be attributed to the tendency of the polymer chains to relieve internal stresses by expanding during swelling in a direction opposite to the direction of movement of the material during compaction. Thus swelling of the polymer chains at right angles to the circumference of the tablet, to cause an increase in tablet thickness, will be accompanied by tensioning in a radical direction which will cause a diminution of the circumference.

TABLE 9: Composition of the Polymers Synthesized for Spray Drying

lactide (%mol) in Monomer Mixture	Lactide (%mol) in Polymer
100.0	100
87.5	85
76.5	75
51.4	50
0.0	0

TABLE 10: Molecular Weight Degradation Half-Lives, $t_{(0.5iv)}$, and Mass Degradation Half-Lives, $t_{(0.5m)}$ for 50:50 (LE:GE % Mol) Polymers

Inherent Viscosity (dl/dg)	$t_{(0.5iv)}$ (weeks)	$t_{(0.5m)}$ (weeks)
0.278	1.4	3.2
0.343	1.6	3.7
0.443	3.1	5.3
0.643	1.9	5.2
0.728	2.1	6.0

TABLE 11: Lag Period and % Mass Loss during Lag Period for Poly(lactide-co-glycolide) Polymers

LE (%mol)	Inherent Viscosity (dl/g)	Lag Period (weeks)	% Mass Loss
50	0.278	0.46	7
50	0.343	1.53	4
50	0.443	2.37	10
75	0.307	1.37	4
75	0.848	5.00	6

% mass loss is approximate value determined from the mass loss versus time plots (Figs. 28, 29 and 31).

TABLE 12: Kinetics of poly(lactide-co-glycolide) hydrolysis

	KINETICS EQUATION								
	$\ln[n]=\ln[n]_o - \alpha k't$			$[n]^{-0.758} = [n]_o^{-0.758} + K_2t$			$[n]^{-1.515} = [n]_o^{-1.515} + K_5t$		
Polymer	$-\ln[n]_o$	$-\alpha K'$	$-r$	$[n]_o^{-0.758}$	K_2	r	$[n]_o^{-1.515}$	K_5	r
100(0.401)	1.239	0.045	0.8970	2.263[α]	0.081	0.9191	4.996[α]	0.445	0.9391
85(0.423)	1.020	0.122	0.9816	1.685	0.390	0.9956	-2.604	3.483	0.9946
85(0.901)	0.174	0.062	0.9744	1.094	0.074	0.9884	1.019	0.237	0.9963
85(1.160)	-0.098	0.045	0.9775	0.908	0.041	0.9879	0.772	0.096	0.9949
75(0.848)	0.265	0.120	0.9271	1.203	0.137	0.3406	1.383	0.415	0.9530

r = correlation coefficient

α For 100(0.401) the kinetics equations were: $[n]^{-0.666} = [n]_o^{-0.666} + K_2t$ and $[n]^{-1.333} = [n]_o^{-1.333} + K_5t$

TABLE 13: Effect of Polymer Composition and Molecular Weight on Yield Pressure, P_Y

LE (%mol)	iv (dl/g)	rate (KN/s)	P_Y (MPa)	CV (%)[a]
100	1.178	0.5	33.24	2.51
85	1.278	0.5	30.27	1.22
85	0.727	0.5	28.43	0.15
85	0.727	1.5	48.69	2.44
85	0.334	0.5	31.35	6.21
75	1.134	0.5	31.61	7.57

The particle size range of the powders was 63-150μ

[a] Coefficient of variance

TABLE 14: Effect of Copolymer Composition (LE% mol) and Molecular Weight (iv) on the Copolymer Contact Angle (θ) with Water

LE (% mol)	iv (dl/g)	Cosθ	θ(°)	C.V. (%)[a]
100	0.820	0.216	77.5	3.96
85	1.278	0.261	74.9	1.34
85	0.727	0.250	75.5	1.37
85	0.334	0.245	75.8	0.89
75	0.796	0.312	71.8	4.57

[a] Coefficient of variance

TABLE 15: Analysis of Variance of Contact Angle Values obtained using Copolymers with different composition

Source of Variation	Sum of Squares	D.F.[a]	Mean Square	F
Composition	33.13	2	16.57	2.33
error	21.30	3	7.10	
total	54.43	5		

[a]Degrees of freedom

$F < F_{2,3\ (0.05)} = 9.55 \Rightarrow H_o$ is valid

TABLE 16: Rate of Water Uptake (% water uptake.day^{-1}) from Poly(lactide-co-glycolide) Matrices during the first week of Immersion in Phosphate Buffer

	POLYMER					
Interval (days)	100(1.178) M_o=221.43	85(1.278) M_o=275.68	85(0.727) M_o=297.80	85(0.308) M_o=195.35	75(1.134) M_o290.23	50(0.343) M_o=241.33
0 - 0.5		2.10	1.94	4.28	1.44	
0.5 -1	0.76$^{\alpha}$	0.50	0.74	1.40	1.10	2.4$^{\alpha}$
1 - 2	0.09	0.28	0.23	0.43	0.67	0.85
2 - 3	0.07	0.16	0.26	1.01	0.30	0.45
3 - 4	0.06	0.18	0.23	0.73	0.32	0.89
4 - 5	0.03	-0.07	0.12	0.69	0.15	0.61
5 - 6	0.06	0.15	0.17	0.54	0.31	0.49
6 - 8	0.03	0.23	0.24	0.65	0.08	0.68

M_o is the initial weight of the matrix in mg

$^{\alpha}$ water uptake at 0-1 day interval.

TABLE 17: Kinetic Analysis of Water Uptake Data up to "Equilibrium" and "Equilibrium" Water Uptake (%).

POLYMER

KINETIC SYSTEM	100(1.178)		85(1.278)		85(0.727)		85(0.308)		75(1.134)		50(0.343)	
	K[a]	r[b]	K	r	K	r	K	r	K	r	K	r
Zero Order	0.072	0.9976	0.237	0.9796	0.225	0.9680	0.707	0.9469	0.386	0.9613	0.660	0.9865
First Order	-0.0003	-0.9961	-0.001	-0.9799	-0.001	0.9680	-0.003	-0.9473	-0.002	-0.9622	-0.003	-0.9865
Higuchi Matrix Model	0.193	0.9914	0.657	0.9967	0.737	0.9927	1.561	0.9723	1.268	0.9908	1.815	0.9961
"Equilibrium" Water Uptake (%)	0.92		1.85		2.18		3.27		2.71		3.72	

K[a] Rate Constant

r[b] Correlation Coefficient

TABLE 18: Effect of Polymer Composition (LE %mol) and Molecular Weight (iv) on the Swelling of Polymers

LE (% Mol)	iv ($dl.g^{-1}$)	Swelling[a]	
100	1.178	18.91	(12.71)[d]
85	1.278	21.49	
85	0.727	26.93	
85	0.308	35.3[b]	
75	1.134	32.05	(27.30)[d]
50	0.343	34.8[c]	(30.56)[d]

a % vertical expansion of tablet after 25 days immersion in phosphate buffer (mean of two replicates)

b approximate value

c approximate value after 20 days immersion in phosphate buffer

d Swelling after 2 days immersion in phosphate buffer

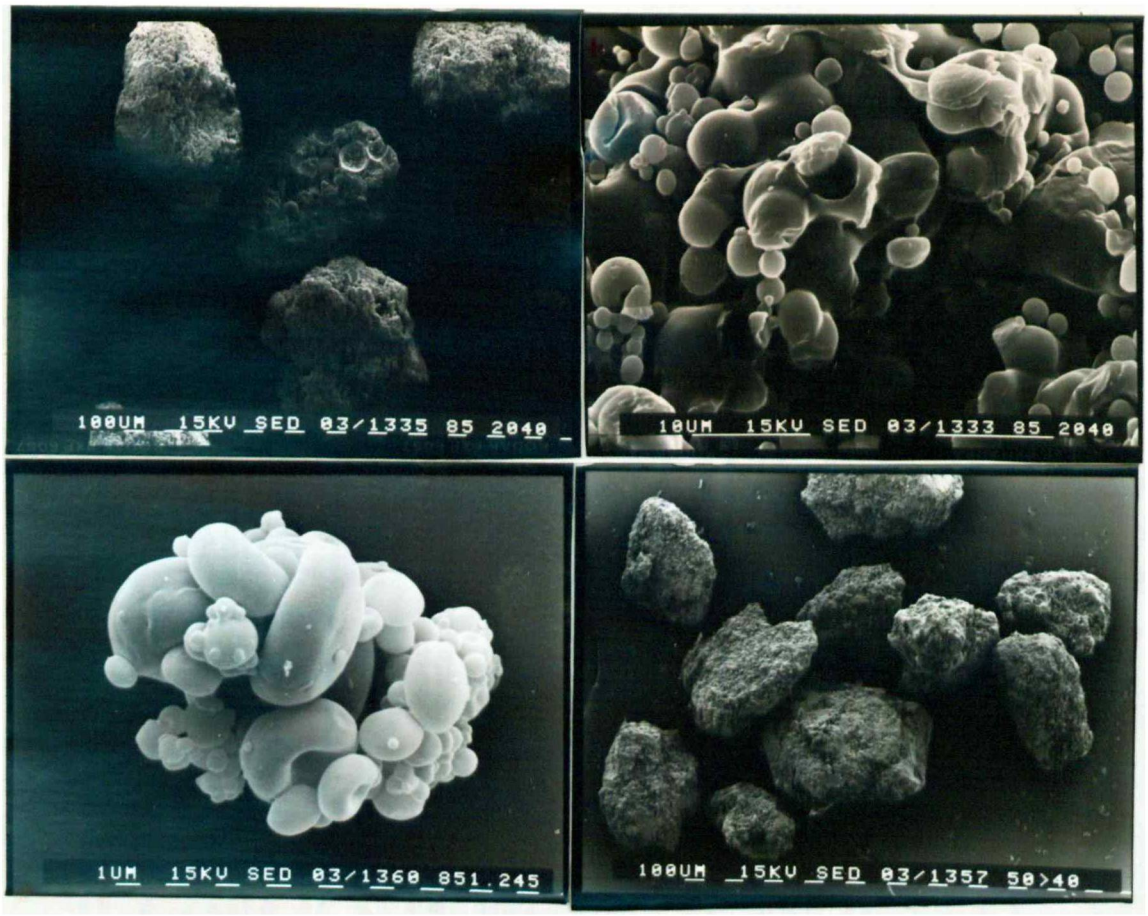


Fig. 24: Scanning Electron Micrographs of Spray Dried Poly(lactide-co-glycolide) particles

1335: Particles (420-841μ) of a 85(.0308) polymer

1333: Detail of the surface of a 85(0.308) particle (420-841μ)

1357: Particles (>420μ) of a 50(.343) polymer

1360: Particle (45-63μ) of a 85(1.278) polymer

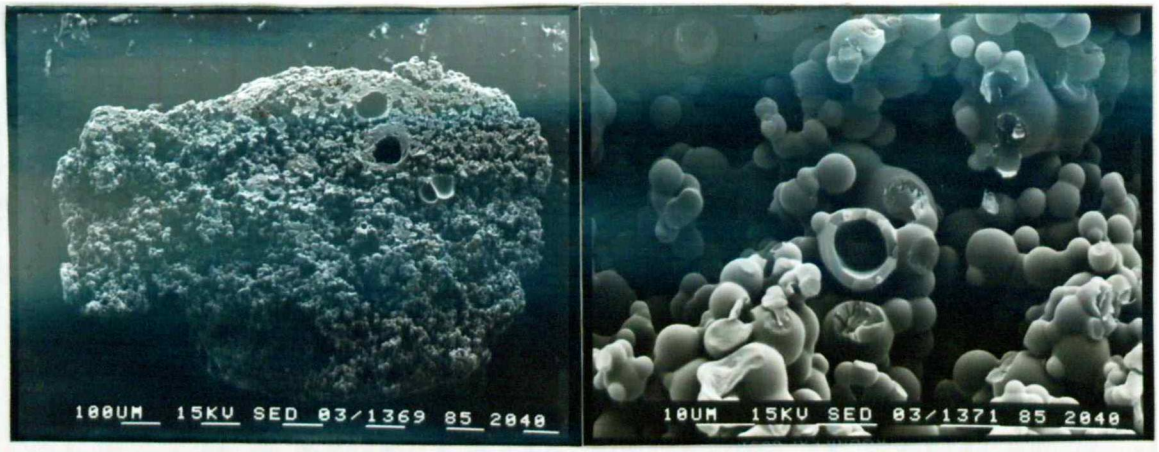


FIG. 25: Scanning Electron Micrographs of the Interior of Spray Dried Poly(lactide-co-glycolide) Particles

1369: Mid-cross-section cut of a 85(0.308) particle (420-841μ)

1371: Detail of the interior of the particle shown in 1369.

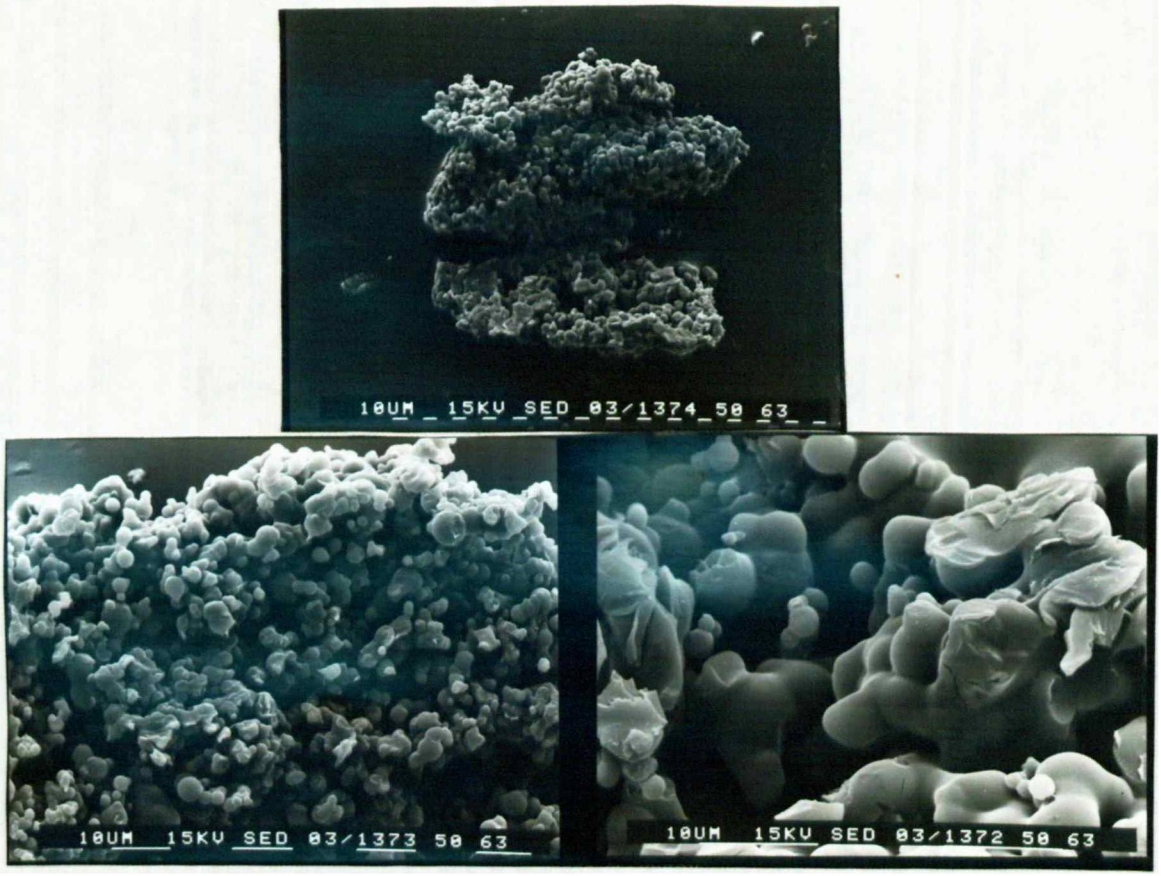


Fig. 26 Scanning Electron Micrographs of the Interior of a 50:(0.343) Particle (63-150μ)

1374: The whole particle split into two portions

1373: The interior of the particle shown in 1374

1372: Detail of the interior of the particle shown in 1374

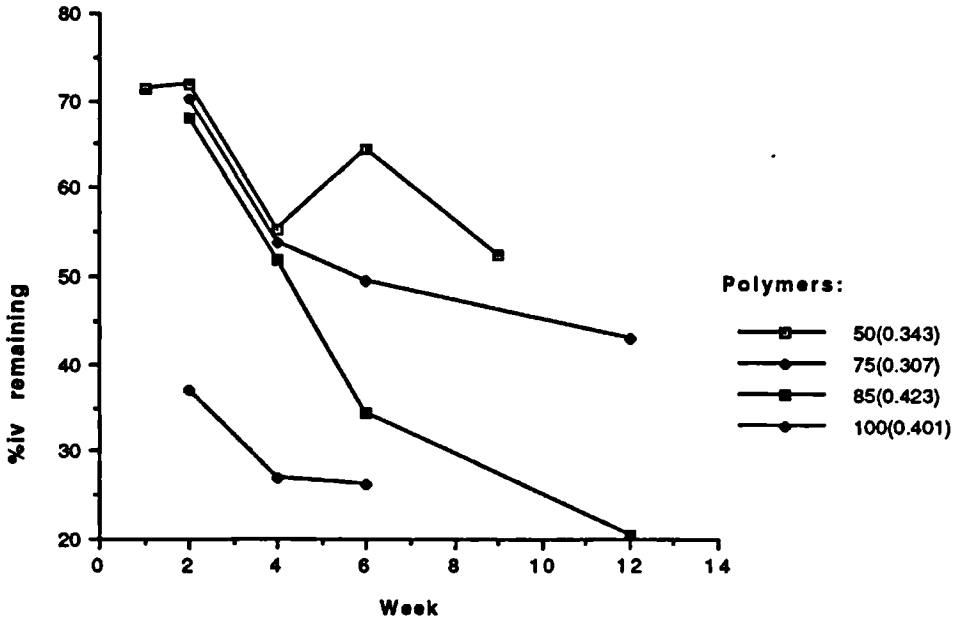


FIG. 27 MW reduction with time profiles for polymers with initial iv 0.3-0.4 (incubation medium: phosphate buffer, pH 7.4).

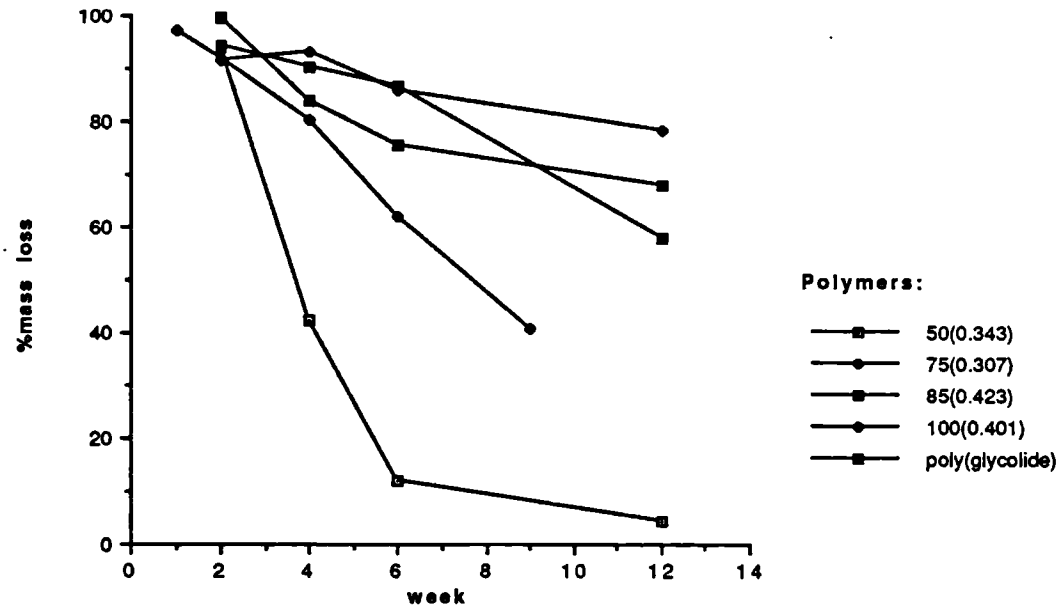


Fig.28 Mass loss with time profiles for polymers of initial iv 0.3-0.4 (incubation medium: phosphate buffer, pH 7.4).

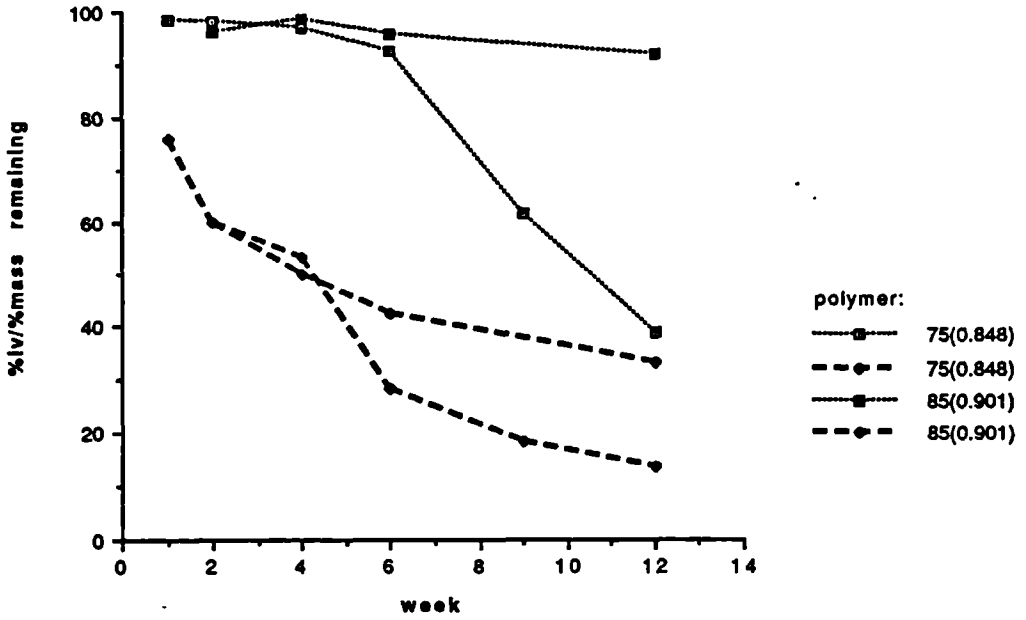


Fig.29 Mass loss and mw reduction with time profiles for polymers with initial iv approx. 0.9 (--- %iv, ···· %mass ; incubation medium: phosphate buffer, pH 7.4).

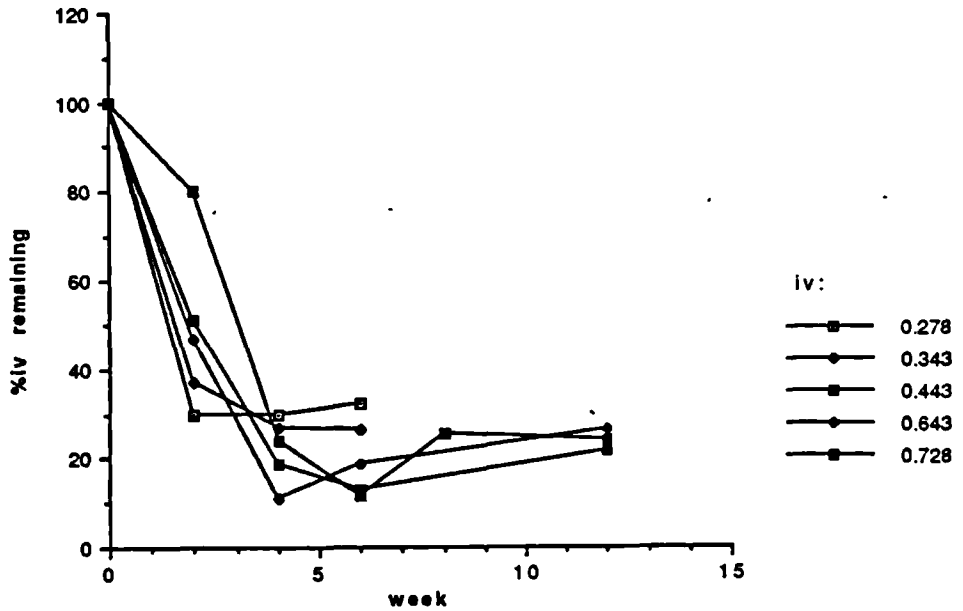


Fig.30 MW reduction with time profiles for 50:50(LE:GE %mol) polymers having different initial iv (incubation medium: phosphate buffer, pH 7.4).

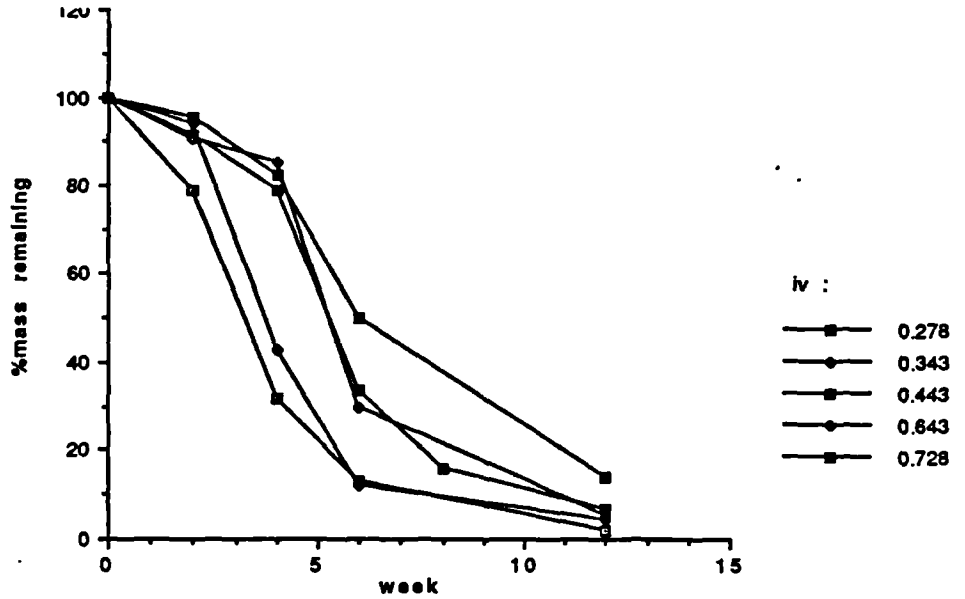


Fig. 31 Mass loss with time profiles for 50:50(LE:GE %mol) polymers having different initial iv (incubation medium: phosphate buffer, pH 7.4).

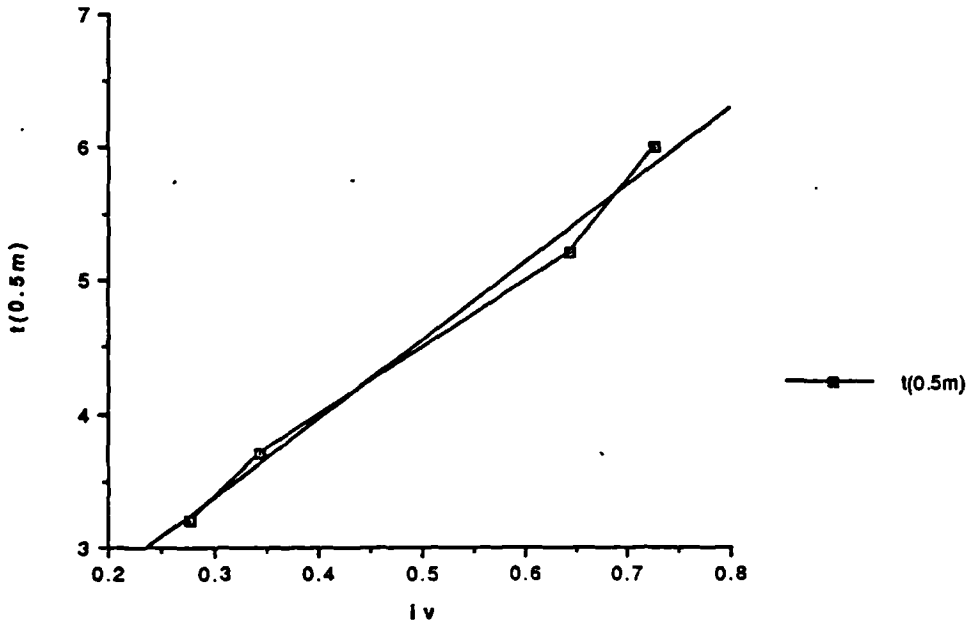


Fig. 32 Effect of polymer mw,iv on the mass degradation half-life ,t(0.5m) of 50:50 (LE:GE %mol) polymers (regression equation: y= 1.6105 +5.8524x ,r= 0.989).

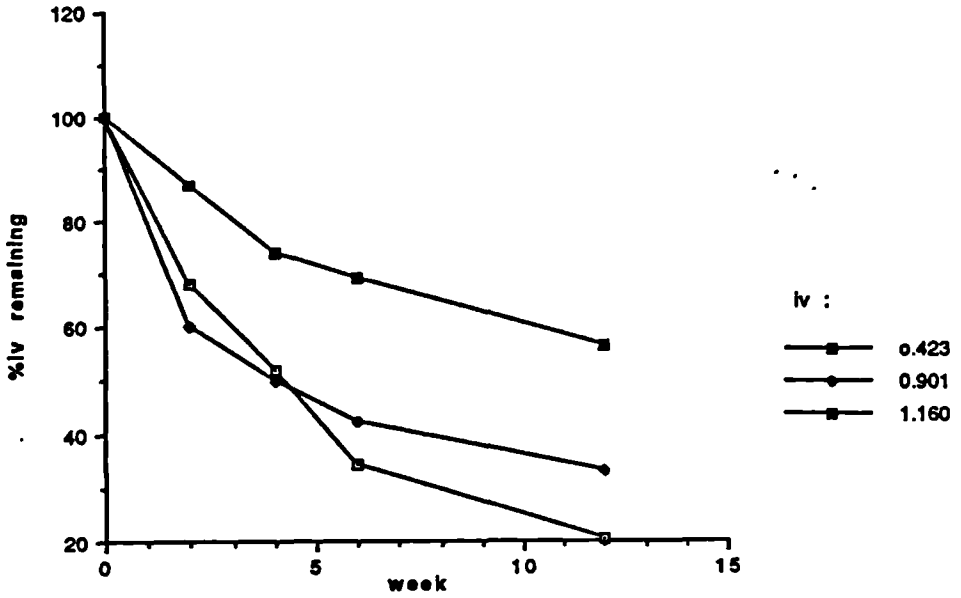


Fig. 33 MW reduction with time profiles for 85:15(LE:GE %mol) polymers having different initial mw (incubation medium: phosphate buffer, pH 7.4).

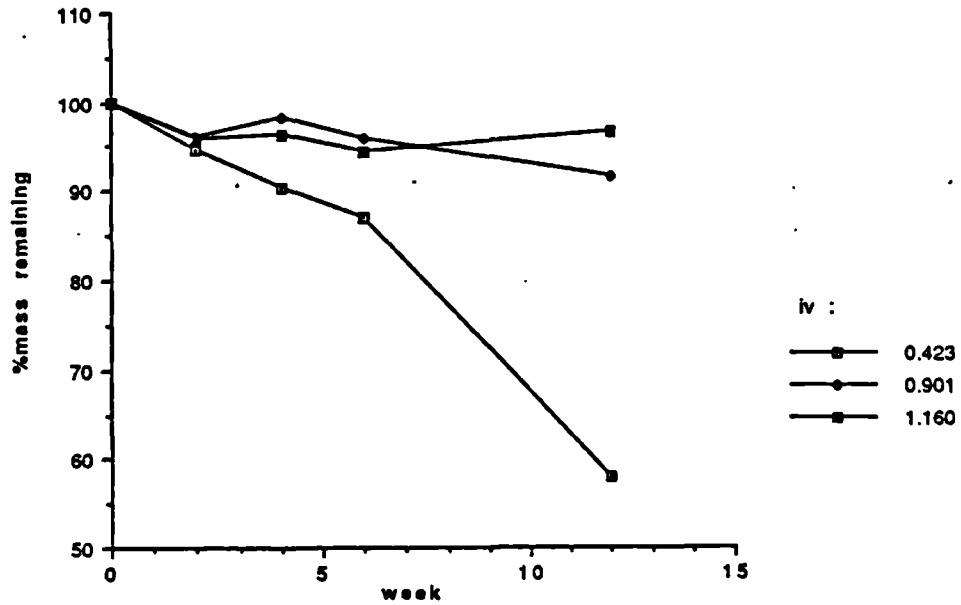


Fig. 34 Mass loss with time profiles for 85:15(LE:GE %mol) polymers having different initial mw (incubation medium: phosphate buffer, pH 7.4).

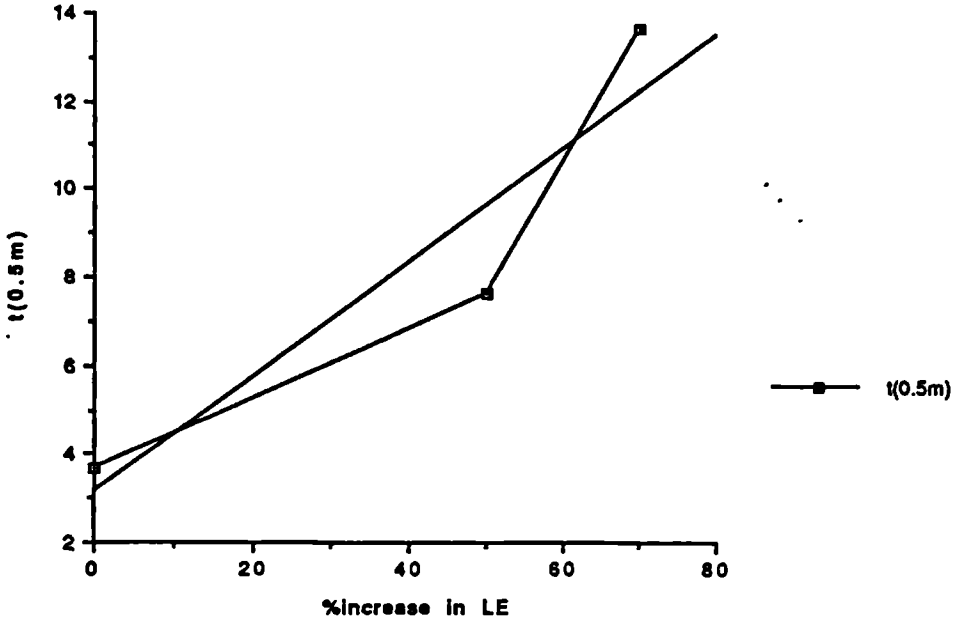


Fig.35 Effect of percent increase in LE content(%mol) on mass degradation half-life,t(0.5m) of polymers (regression equation: y=3.1308 + 0.12923x , r= 0.873).

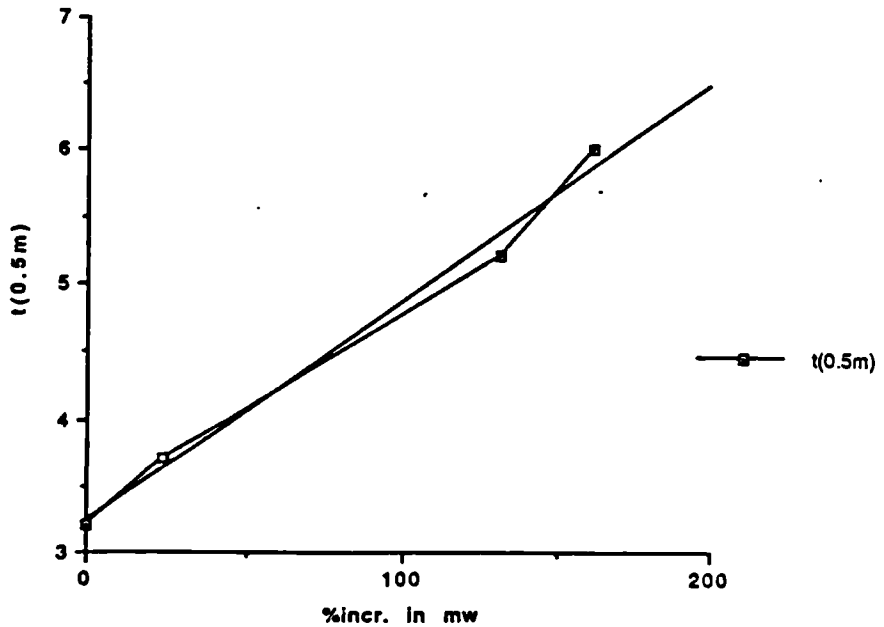


Fig. 36 Effect of %increase in mw on mass degradation half-life, t(0.5m) of polymers (regression equation: y=3.2375 + 0.0162x , r= 0.989).

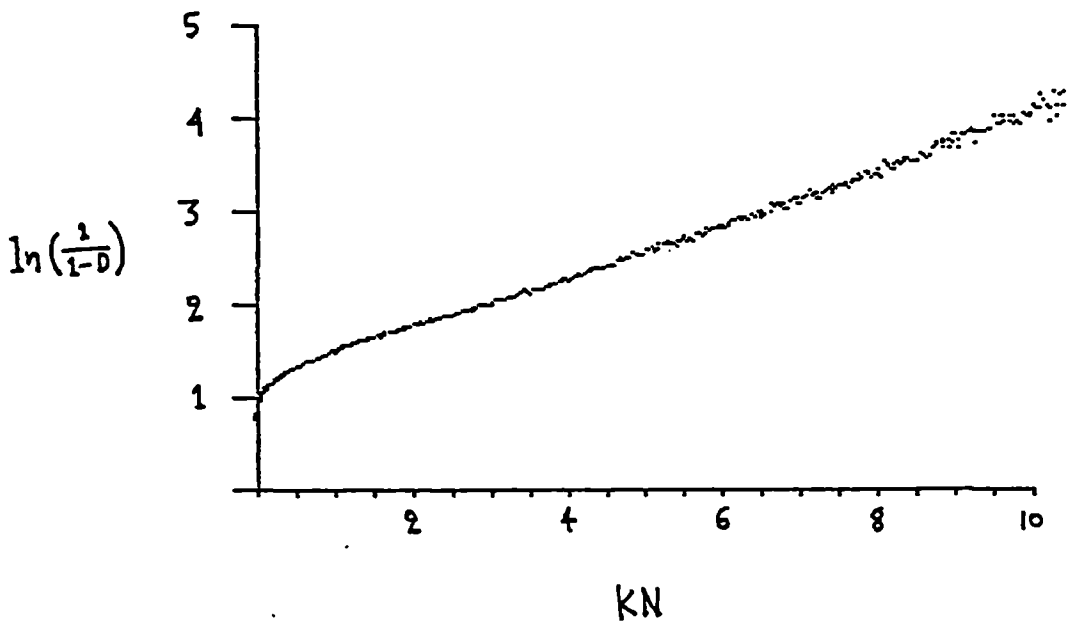


Fig. 37 Heckel plot of a 75(1.134) polymer (particle size range 63-150 μ, compaction rate 0.1 KN/s).

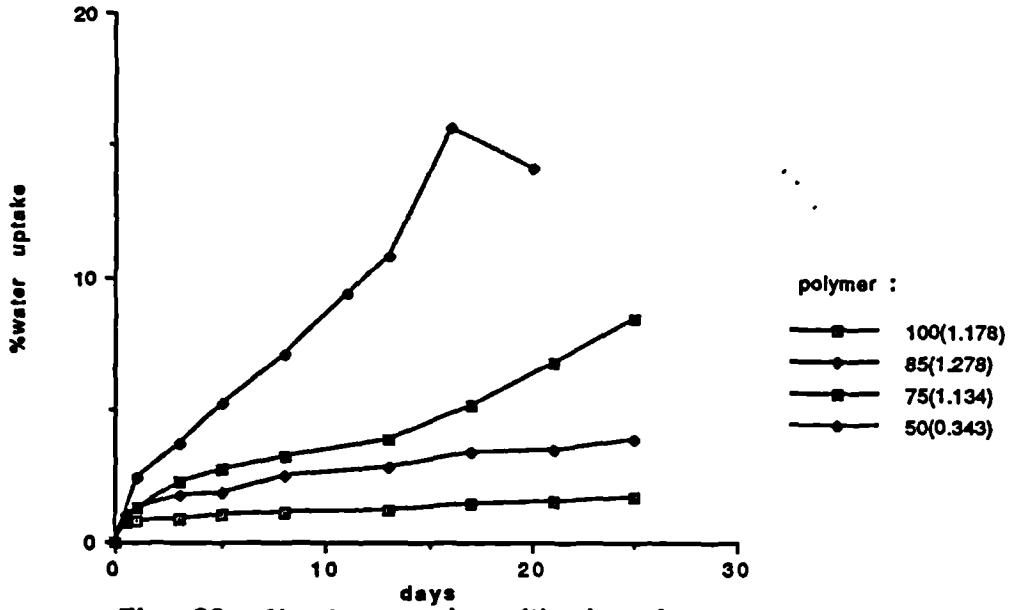


Fig. 38 %water uptake with time for polymers having different composition (incubation medium: phosphate buffer, pH 7.4).

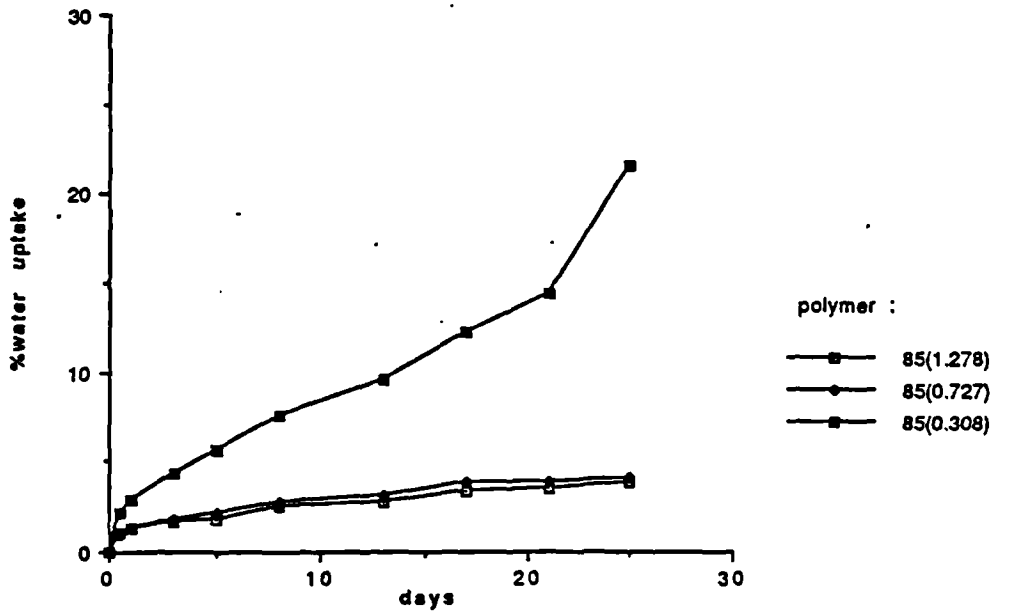


Fig. 39 %water uptake with time from 85:15(LE:GE %mol) polymers having different mw (incubation medium: phosphate buffer, pH 7.4).

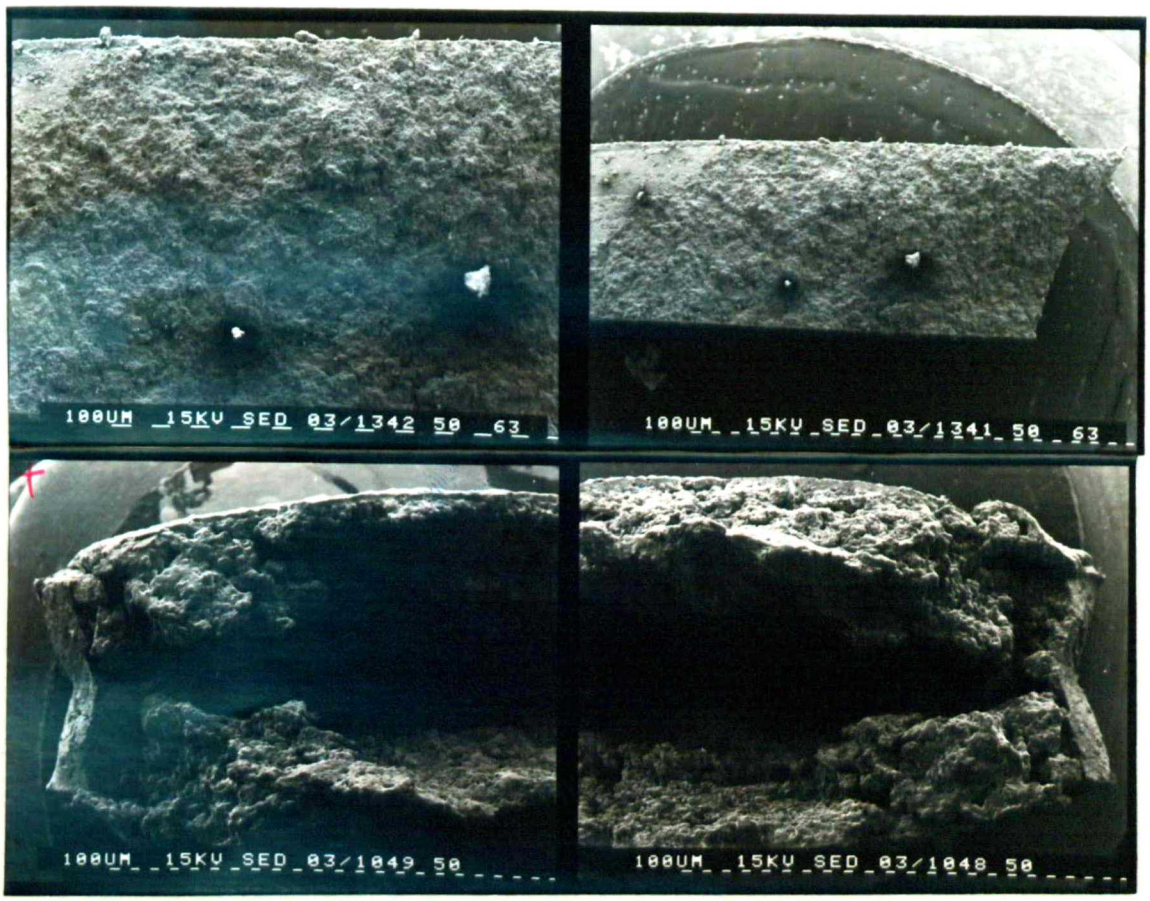


Fig. 40 **Scanning Electron Microscope of 50(0.343) Matrices (prepared by compressing polymer powders of 63-150μ at 10 KN) Before and After 20 days Incubation in Phosphate Buffer, pH=7.4.**

1341, 1342: Mid cross-section cut of the matrix before incubation

1048, 1049: Matrix appearance at the end of incubation period.

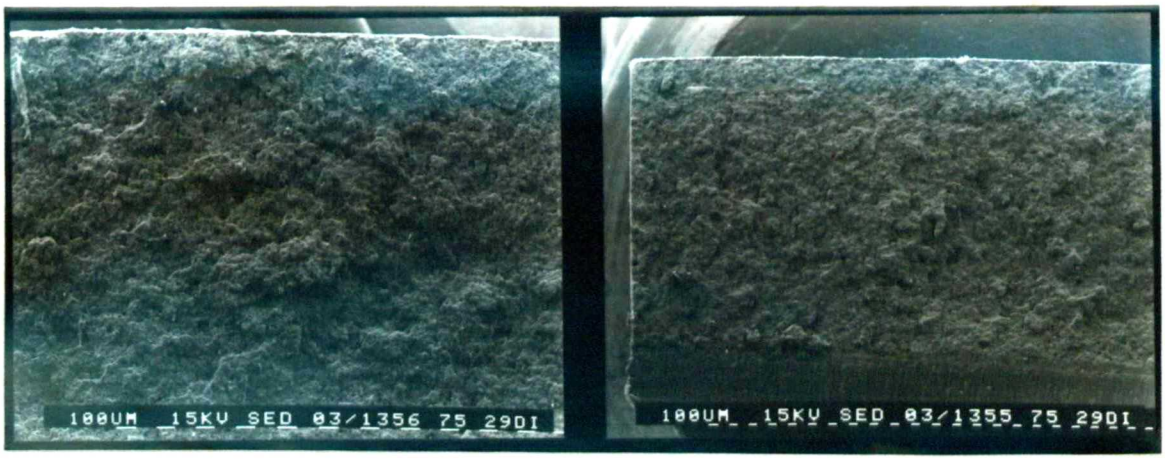


Fig. 41 **Scanning Electron Micrographs of 75(1.134) Matrices (prepared by compressing polymer powders of 63-150μ at 10 KN) After 25 Days Incubation in Phosphate Buffer, pH=7.4**

1355, 1356: Mid cross-section cut of the matrix after incubation.

4.PREPARATION AND CHARACTERIZATION OF POLY(LACTIDE-CO-GLYCOLIDE) MATRIX TABLETS

4.1 Introduction

One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blends of drug, polymer, and additives to form a tablet in which drug is embedded in a matrix core of polymer.

In this chapter, spray dried poly(lactide-co-glycolide) powders were used to prepare phenobarbitone matrix tablets. Short (48 hours) release experiments *in vitro* were carried out to investigate the effects of technological factors, such as compaction force, particle size and drug : polymer ratio, on drug release and on the mechanical strength of the tablets. The combination of formulation variables giving satisfactory low initial drug release was then used to prepare tablets for longer term investigation of the effects of polymer characteristics on drug release. The prospect of using poly(lactide-co-glycolide) matrix tablets for the long term controlled delivery of bioactive agents was considered.

4.2 Materials and Methods

4.2.1 Materials

Poly(lactide-co-glycolide) polymers, phenobarbitone (Sigma minimum assay 99%), sodium phenobarbitone (Fluka, minimum assay 99%), magnesium stearate (BDH, GPR) and chloroform (FSA, analar) were used.

4.2.2 Methods

4.2.2.1 Preparation of Tablets

Drug and polymer powders of the same size particle fraction were mixed in a tumbling blender (Pascall Engineering England). A mixing time of 30 minutes was found to produce homogenous drug-polymer mixtures. These were compressed in the Dartec apparatus to obtain tablets of approximately 220 mg. A compaction force of 10 KN was normally applied, the rate and dwell time being maintained at 1 $KN.s^{-1}$ and 15s respectively. Unless otherwise specified the drug polymer mixtures consisted of 25% drug by weight.

4.2.2.2 Drug Release Properties of Tablets

Drug release from the polymer matrices was investigated using a USP XXII (1990) automated dissolution apparatus. The apparatus consisted of a water bath (Copley dissolution bath), spectrophotometer (Philips Pye Unicam 8620 UV/VIS/NIR) and attached cell changer with an Opus PCIII coupled to the spectrophotometer. The PU8260 TDS version I.2 Philips Scientific, 1987 (England) software was used to program the operation of the dissolution system and to perform data capture and analysis.

1L of phosphate buffer, pH = 7.4, was used as dissolution medium. The stirring rate was maintained at 50 rpm and the temperature at $37^{o}C$. The dissolution medium was assayed, both for phenobarbitone and sodium phenobarbitone, at 240 nm.

Automated release experiments were conducted for 48 hours, with manual sampling for longer experiments. All release determinations were carried out at least in duplicate. A Minolta SKT 101 (Japan) camera attached to a Nikon Labphot (Japan) microscope was used to take pictures of tablets after dissolution. SEM pictures of tablets before and after dissolution were also taken.

4.2.2.3 Mechanical Properties of Tablets

The diametral breaking strength of tablets was measured using a CT40 tester (Engineering System, Nottingham). Their tensile strength (T) was determined from the formula (Fell and Newton 1970):

$$T = \frac{2P}{\pi dl}$$

Equation 43

where P is the force causing fracture, d is the tablet diameter and l is the tablet thickness.

4.3 Factors Investigated Affecting Drug Release from Poly(lactide-co-glycolide) Matrix Tablets

4.3.1 Factors Related to Formulation

The effects of the following formulation variables were investigated:

I. Compaction force: Five forces were used: 2.5, 5, 10, 20 and 30 KN. These corresponded to 28.60, 57.20, 111.44, 228.78 and 343.17 MPa compaction pressures

respectively. The effect of compaction force was examined at 43-63μ and 250-420μ particle size fractions of the drug-polymer powder mixtures.

II. Particle size fraction: Four particle size fractions were used: 45-63, 63-150, 150-250, and 250-420μ.

III. Drug proportion in the matrix (% weight): three proportions were examined: 12.5, 25 and 50%.

4.3.2 Factors Related to the Polymer

The effects of changing the following polymer properties were investigated:

I. Polymer molecular weight: three molecular weights of a 85:15 (LE:GE %mol) polymer were studied. The polymers had 1.278, 0.727 and 0.308 inherent viscosities.

II. Polymer composition: four lactide: glycolide molar ratios were examined: 100:0, 85:15, 75:25, and 50:50. The tablets were prepared from 150-250μ powders using 10 KN forces at 1 KN.s^{-1} rate.

4.4 Results and Discussion

4.4.1 Effect of Formulation Factors

The effects of compaction force were investigated using a 85(0.727) polymer. The rate of phenobarbitone release

decreased with an increase in compaction force. The effect was more pronounced with tablets prepared using powder mixtures of large particle size, 250-420μ (Figs. 42 and 43).

As negligible degradation takes place during the first 2 days, drug release can be described by Higuchi's rate law (Higuchi, 1963):

$$Q = \left[\frac{D\epsilon}{t}(2A - \epsilon C_s)\, C_s t\right]^{0.5}$$

Equation 44

Where Q is the amount of drug released after time t per unit exposed area, D = the diffusion coefficient of the drug in the dissolution medium t and ϵ are the tortuosity and porosity of the matrix respectively, A is the amount of drug per unit volume, and C_s the solubility of drug in the dissolution medium.

Increasing the compaction pressure causes a decrease in the porosity of the matrix (Table 19), and according to Equation 44 a lower rate of drug release results. It was shown (paragraph 3.3.4) that poly(lactide-co-glycolide) is a soft and ductile material, which explains the low porosity values obtained, even at low compression (Table 19). The porosity of the tablets prepared for the 45-63μ powders did not change significantly at compaction forces higher than 5 KN (Table 19) which accounts for the small differences in the rate of drug release between tablets prepared using compaction forces higher than 5 KN (Fig. 43).

When the same compaction pressure was applied the matrices prepared from powders with a small particle size fraction (45-63μ resulted in a lower porosity than those matrices prepared from large particles, size fraction 250-420μ (Table 19). This is probably because small particles are capable of higher densification through interparticulate slippage and rearrangement than large particles. Similar results have been obtained during compaction studies involving crystalline and spray dried lactose (Fell and Newton, 1970). Because of their lower porosity, matrix tablets prepared from the smaller particle size range exhibited slower drug release rates than those prepared from the larger particle size range using the same compaction pressure (Figs. 42 and 43).

Sustained release matrix tablets should have adequate mechanical strength to withstand shocks during handling, shipping and dispensing. Nor should disintegration of the matrix occur during drug delivery. Tablets with high tensile strength values were obtained, even with low compression pressures, due to the high plasticity of the spray dried polymers. Soft, ductile materials, such as poly(lactide-co-glycolide), deform extensively during compaction causing a high interparticulate area of contact and therefore strong interparticulate bonding, leading to the formation of strong compacts. The tensile strength of the tablets did not change significantly at compaction forces higher than 20 KN (Table 20).

The effect of the particle size fraction of the drug-polymer powders on drug release was investigated using a 75(1.134) polymer. A compaction force of 10 KN was employed. An increase in the particle size fraction caused an increase in the rate of release (Fig. 44), probably because, for a given compaction pressure, increasing the particle size of the powder undergoing compression results in compacts with higher porosity (Table 19). However, only relatively small differences in drug release rates were obtained by changing particle size, probably due to the loose and porous texture of the spray dried polymer particles. This decreases considerably the resistance of the particles to deformation, reducing the significance of particle size on the properties of these tablets.

An increase in phenobarbitone content (% weight) in the matrix caused a significant increase in the amount of phenobarbitone release. The amount of phenobarbitone released in 48 hours increased from 10.39 to 36.49% when the amount of phenobarbitone in the matrix increased from 12.5 to 50% (Fig. 45).

According to Higuchi's relationship (Equation 44) an increase in the amount of the drug in the matrix (A) should cause an increase in the rate of drug release. It should also cause an increase in the porosity of the leached portion of the matrix (ϵ), which in turn would further increase drug release rate. The porosity of the leached portion of the matrix is given by (Higuchi, 1963):

$$\epsilon = \epsilon_o + V_s A$$

Equation 45

Where ϵ_o is the initial matrix porosity, V_s is the specific volume of the drug, and A is the amount of drug per unit matrix volume.

The results obtained (Figs. 42 to 45) show that the rate of drug release is affected by the change in formulation variables, and that the effects of changing any particular variable (e.g. compaction force) could depend on the level of the others (e.g. particle size). The rate of drug release can be diminished by increasing the compaction force, by decreasing the particle size of the drug-polymer mixture, or decreasing the proportion of the drug in the matrix. However, exceedingly high compaction forces, or very small particle sizes, should be avoided since the former increases the wear of tableting machines and the latter the powder cohesiveness. It was observed that the larger particle sizes (150-250μ and 250-420μ) flowed into the dye of the Dartec instrument more readily and packed more uniformly than the smaller particle sizes. A compaction force of 10 KN, combined with a particle size fraction of 150-250μ, gave a satisfactory low initial drug release so that formulations prepared under these conditions were used to investigate the effects of polymer characteristics.

4.4.2 Effect of Polymer Characteristics

The effect of changing the polymer composition and molecular weight on the release of phenobarbitone from poly(lactide-co-glycolide) matrix tablets *in vitro* was investigated. Drug release followed for more than 30 days. The release of phenobarbitone was significantly sustained (Figs. 46, 48 and 50).

Drug release profiles consisted of three regions. An initial region of relatively high release rate, probably due to the rapid leaching of drug from surface layers of the tablet (burst effect), followed by an extended region of lower but essentially constant release rate (steady state release region), which appeared to last approximately until the time required for 80% of the drug to be released. The steady state release region was followed by a final region in which the rate of drug release fell off as exhaustion of drug in the matrix approached [Fig. 46, release profile of 75(1.134) matrices and Fig. 48, release profile of 85(0.727) matrix].

Plotting the rate of drug release against time (Figs 47, 49 and 50) showed that the rate remained essentially constant between approximately 20 and 80% release, suggesting that drug release did not follow the matrix release mechanism suggested by Higuchi (1963). It was found that the polymers swell upon immersion in an aqueous environment (paragraph 3.3.6.). Swelling of the polymer particles may reduce the volume of water filled pores and channels available for drug diffusion or may even create blind

aqueous domains inside the matrix (Fig. 51). (The pores in the matrices are considered to fill with water very rapidly as indicated by the rapid release of sodium phenobarbitone, which is almost complete after 3 hours, Fig. 52). Diffusion through the swollen polymer may then become the predominant release mechanism.

The rate of diffusion in the swollen polymer is much lower than that in water because polymer chains impose severe restrictions in drug movement and this, together with the decrease in drug diffusion rate via aqueous capillaries and pores due to the decrease in pore volume caused by polymer swelling, probably accounts for the significantly sustained release of phenobarbitone from the matrix tablets. Degradation and water uptake with time cause an increase in drug release rate, the former generating aqueous channels through which drug diffusion and release can occur, and the latter because drug diffuses mainly through the aqueous regions of a polymer membrane (Langer and Peppas, 1981). The increase in drug release rate with time caused by degradation and water uptake compensated for the decrease in release rate caused by the increase in the distance with time which the drug has to travel to be liberated, and so an essentially constant rate of drug release resulted (Figs. 47, 49 and 50).

An increase in the glycolide content of relatively high mw polymers caused an increase in drug release rate (Fig. 46), due to an increased water uptake and swelling, which facilitates drug diffusion through the polymer. A

concomitant increase in the polymer degradation rate with an increase of glycolide content will also contribute. SEM pictures of mid-cross-section tablet cuts before and after dissolution confirmed that the 75(1.134) polymer was more degraded after dissolution than the 100(1.178) polymer (Figs. 53 and 54). The 100(1.178) polymer did not appear to undergo significant degradation over the 33 day period. After dissolution this polymer appeared to retain a continuous matrix having relatively few pores. Phenobarbitone crystals embedded in the matrix could still be observed (Fig. 54)

Comparison of the steady state drug release constants, calculated by fitting the release data in the steady state region of the curves to zero order rate equations, revealed that the introduction of 25% mol glycolic acid units in the polymer chains increased the rate of drug release by a factor of approximately 3 (Table 21).

A decrease in polymer molecular weight was shown to increase swelling, water uptake and degradation rate (paragraphs 3.3.3 and 3.3.6), and it would therefore be expected that by decreasing the molecular weight an increased drug release rate would result. This was indeed the case when the inherent viscosity of a 85:15 (LE:GE %mol) polymer decreased from 1.278 to 0.727, but a further decrease in the inherent viscosity to 0.308 brought about the opposite effect, i.e. a decrease in the rate of drug release (Figs. 48 and 49). This can be attributed to the rapid hydrolysis of the low mw polymer, which gradually

transformed the interior of the matrix to a hydrogel (Fig. 56). For release to occur the drug had to diffuse through that gel so that only one release mechanism operated, whilst in the case of high mw polymers drug release could occur by both diffusion through aqueous channels and diffusion through the swollen polymers (Fig. 51).

The transformation of the central portion of the tablet into a hydrogel had already started after 10 days dissolution. The gel area had cavities due to erosion of the polymer. After 20 days the dimensions of the cavities increased and a large number of tiny holes covered the gel area. Significant degradation of the surface layers of the matrix could also be observed. After 28 days immersion in phosphate buffer gelation of the tablet centre was complete; the interior of the tablet was then a soft, gummy and sticky material (in the SEM pictures the gel formed after 28 days appears to be "inflated" because of water evaporation out from the gel during evacuation of the SEM sample compartment) (Figs. 55 and 56). The gel became thinner with time, and its rather loose texture after 31 days dissolution is shown in Fig. 57.

Similar phenomena to that observed with the 85(0.308) polymer occurred with a low mw 50:50 (LE:GE %mol) polymer (Figs. 58 and 59). However, gelation of the central portion in the 50(0.343) matrices proceeded more slowly than in the 85(0.308) matrices, as comparison of the gel texture in Figs. 56 and 59 shows, possibly because the 50(0.343) polymer had a slightly higher initial mw than the

85(0.308) polymer. The surface layers of the 50(0.343) matrices appeared to be more degraded than the 85(0.308) matrices after 28 days dissolution. (Comparison of micrographs 1406, 1407 with micrographs 1417, 1418 in figs. 56 and 59). Both the higher mass loss rate, creating a more porous structure in the surface layers of the tablets and the smaller extent of central portion gelation, resulting in an extension of the period during which drug diffusion from the tablet interior through aqueous pores occurs, probably account for the higher rate of drug release observed with the 50(0.343) matrices. The steady state release rate constants were 0.78 and 1.24% released x day^{-1} for the 85(0.308) and the 50(0.343) tablets respectively. These values were lower than the rate obtained from polymers with much higher molecular weights. The 85(0.308) polymer exhibited the lowest rate of drug release from all polymers studied and only poly(lactide), sample 100(1.178) had a lower drug release rate than 50(0.343) polymer over the 33 days study period (Table 21).

From the results obtained (Figs. 46, 48 and 50) it can be deduced that drug release from poly(lactide-co-glycolide) matrix tablets can be controlled by modifying the polymer properties. However, this can be more easily accomplished by modifying the composition of relatively high mw polymers rather than by changing the molecular weight of the polymer. Drug release appears to involve, besides diffusion through the water filled pores, diffusion through the swollen polymer where the size of the drug molecule may be expected to exert a significant influence on the release

rate, because diffusion in polymers is much more sensitive to the molecular weight of the permeant molecules than is diffusion in liquids.

In all cases the initial stage of release (burst stage) lasted 2 days and the amount of drug released during that period tended to increase with the hydrophilicity of the matrix, i.e. with an increase in the glycolide content, or a decrease in the polymer mw, ranging from 15 to 32% (Figs. 46, 48 and 50). Comparison of these results with the results obtained in the study of technological factors (paragraph 4.4.1) indicates that the amount of drug released during the initial burst stage was primarily a function of technological factors rather than function of characteristics.

Drug release from many poly(lactide-co-glycolide) systems has been reported as biphasic or discontinuous. Pitt *et al.* (1979) reported that the release of progesterone from films prepared from polymers with relatively high glycolide content increased abruptly and significantly after approximately 5% release had occurred (20 - 30 days), due to film fragmentation and exposure of a larger surface area. Beck *et al.* (1983$_a$) also found that the release of norethisterone from poly(lactide-co-glycolide) microcapsules was biphasic. Initially, the microcapsules released the drug by diffusion but later degradation of the polymer induced a second phase of release producing increased norethisterone serum levels. The release levels of LHRH analogues from poly(lactide-co-glycolide) depots

was reported to be both biphasic and discontinuous. During the initial phase the polypeptide was released by leaching from the surface of the formulation, whilst during the second phase the polypeptide release occurred by diffusion through aqueous channels generated by polymer degradation. The two phases were separated by a period of subeffective, or no polypeptide release, unless very low mw polymers with high glycolide content and high drug contents were used (Hutchinson and Furr, 1985; Sanders *et al.*, 1986). The release of levonorgestrel from small cylinders prepared using a 90:10 (l-LE:GE %mol) high mw polymer was also reported to be biphasic, but no explanation for this was given (Wise *et al.*, 1980).

With respect to the above reports the continuous and essentially constant release rate obtained with the poly(lactide-co-glycolide) matrix tablets would appear to provide a significant improvement.

TABLE 19: Effect of Compaction Force (F) on the Porosity (ϵ) of 85(0.727) - Phenobarbitone Matrix Tablets

Particle Size Range (μ)	F(KN)	(ϵ)
250 - 420	2.5	0.245
	5	0.145
	10	0.079
	20	0.046
45 - 63	5	0.114
	10	0.051
	20	0.031
	30	0.031

TABLE 20: Effect of Compaction Force (F) on the Tensile Strength (T) of 85(0.727) - Phenobarbitone Matrix Tablets.

F(KN)	Breaking Load* (Kg)	T (MPa)
2.5	7.77	1.64
5	19.31	4.55
10	33.03	8.47
20	38.29	9.84
30	38.53	10.21

Particle size range of drug-polymer mixtures, 45-63μ.

T values are the mean of three replicates.

*CT40 tester indication.

TABLE 21: Steady State Release Rate Constants (K_{SS}) of Phenobarbitone from Poly(lactide-co-glycolide) Matrix Tablets.

Polymer	K_{SS} (% released. day^{-1})	r
100(1.178)	1.19	0.9990
85(1.278)	1.93	0.9981
85(0.727)	2.37	0.9973
85(0.308)	0.78	0.9754
75(1.134)	3.50	0.9961
50(0.343)	1.24	0.9971

Each K_{SS} value is the mean of two determinations;
r = correlation coefficient.

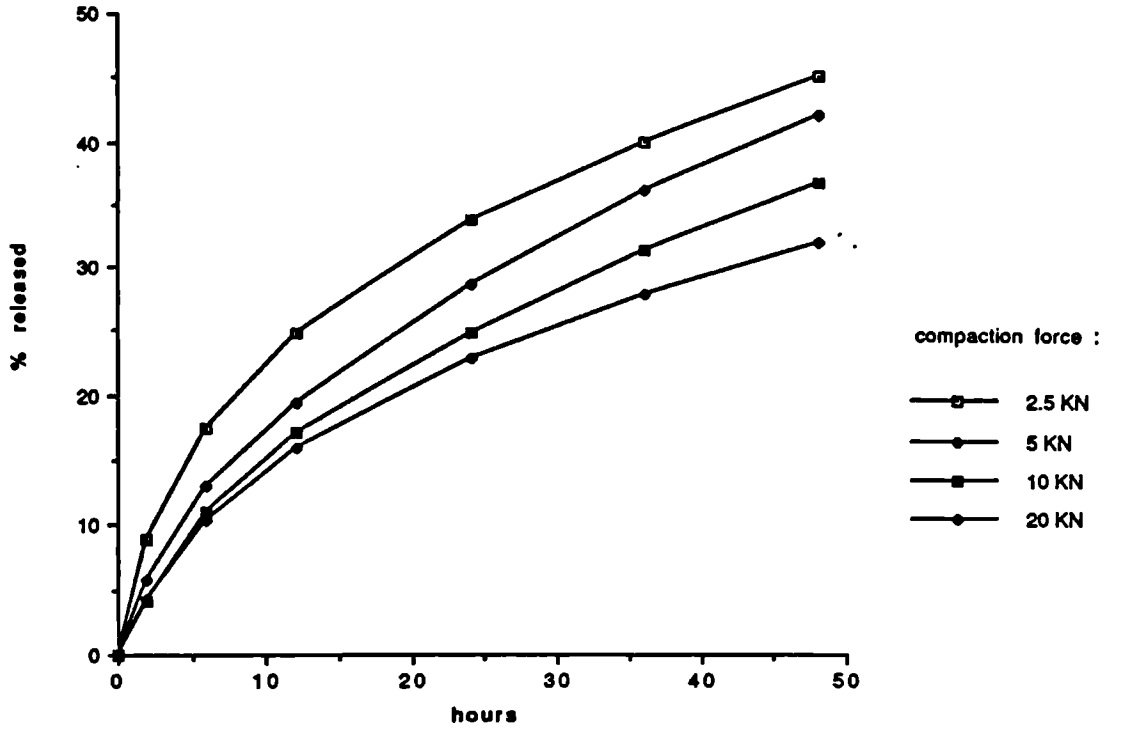


Fig. 42 Plots of phenobarbitone release from 85(0.727) matrices(250-420μ) prepared using different compaction forces (dissolution medium: phosphate buffer ,pH=7.4, 37° C ; stirring rate: 50 rpm).

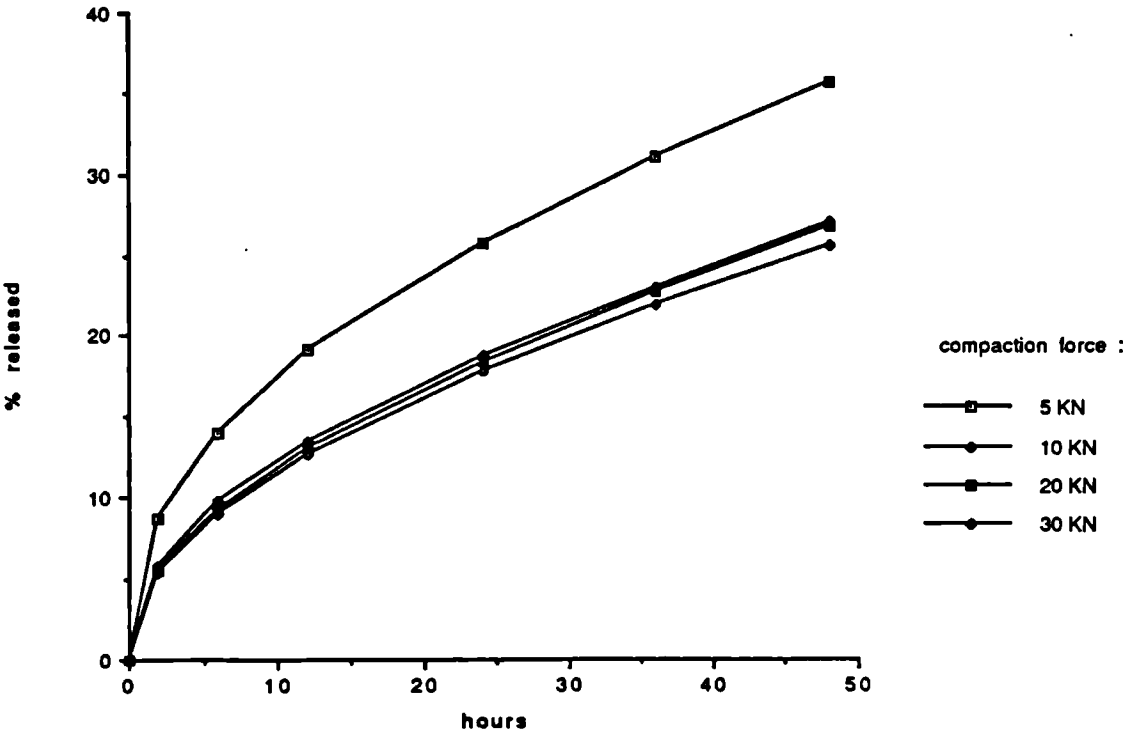


Fig. 43 Plots of phenobarbitone release from 85(0.727) matrices (45-63μ) prepared using different compaction forces (dissolution medium: phosphate buffer ,pH=7.4, 37° C ; stirring rate: 50 rpm).

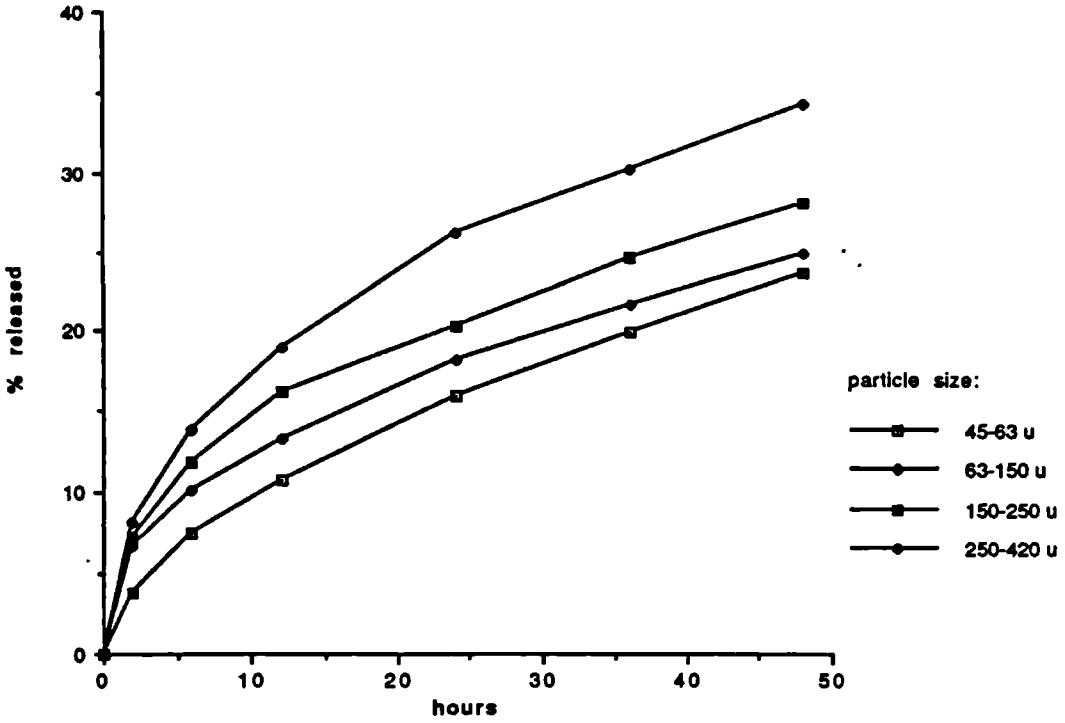


Fig. 44 Phenobarbitone release from 75(1.134) matrices prepared by compressing at 10 KN drug-polymer mixtures of different particle size (dissolution medium: phosphate buffer, pH=7.4, 37° C ; stirring rate: 50 rpm).

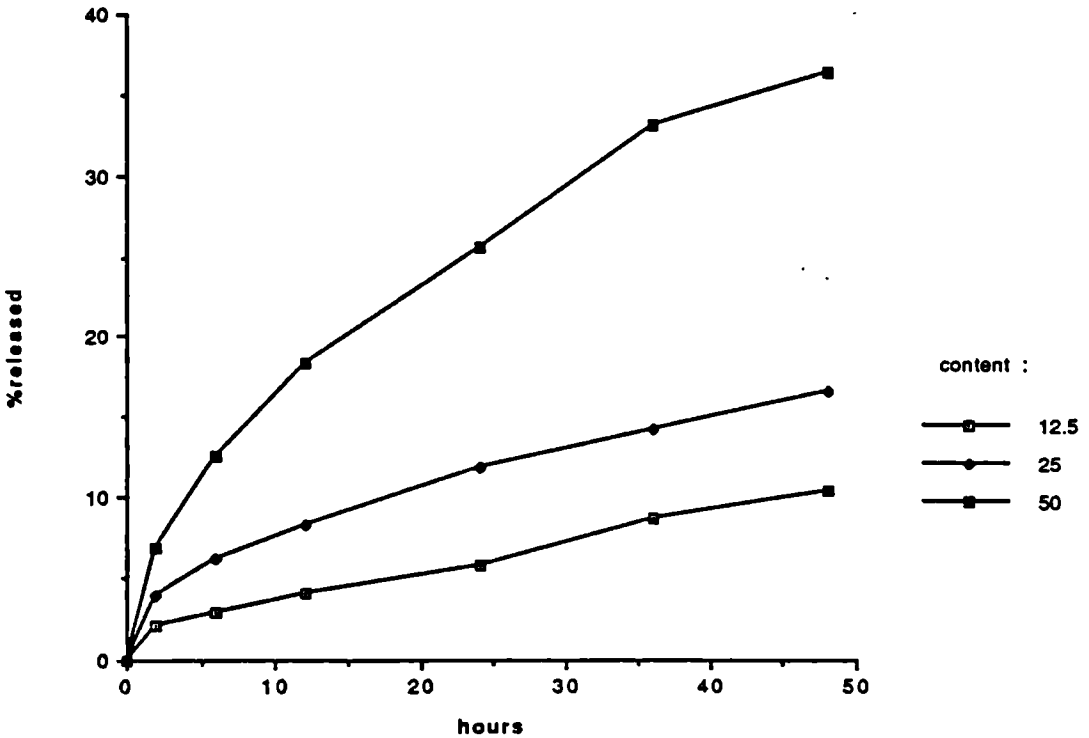


Fig. 45 Drug release plots from 85(1.278) matrices with different phenobarbitone content (%w/w) (dissolution medium: phosphate buffer,pH=7.4, 37° C ; stirring rate 50 rpm.)

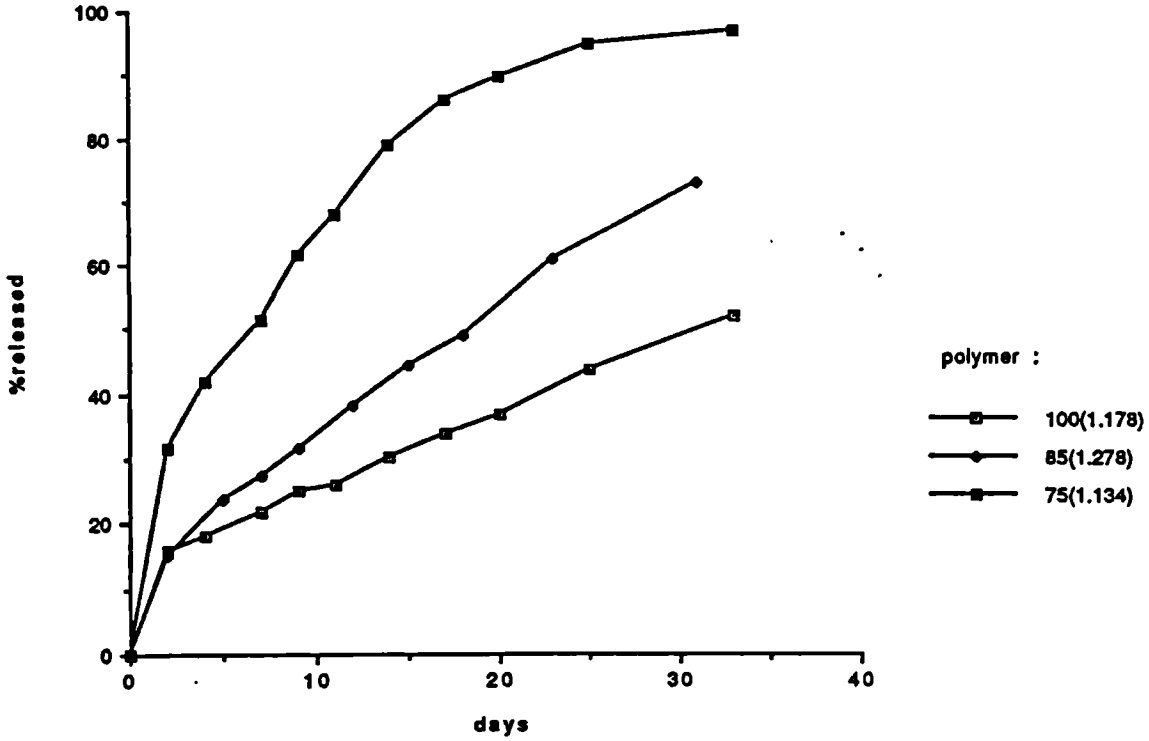


Fig. 46 Plots of phenobarbitone release from polymer matrices having different composition (dissolution medium : phosphate buffer,pH=7.4, 37° C ; stirring rate: 50 rpm)

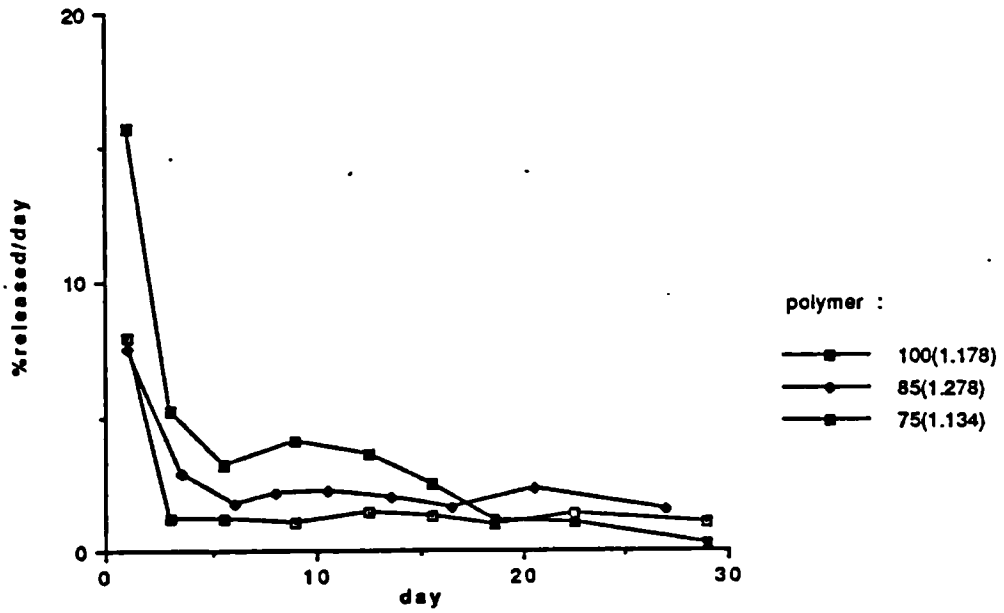


Fig. 47 Rate of phenobarbitone release from polymer matrices having different composition (dissolution medium: phosphate buffer,pH=7.4, 37° C ; stirring rate: 50 rpm).

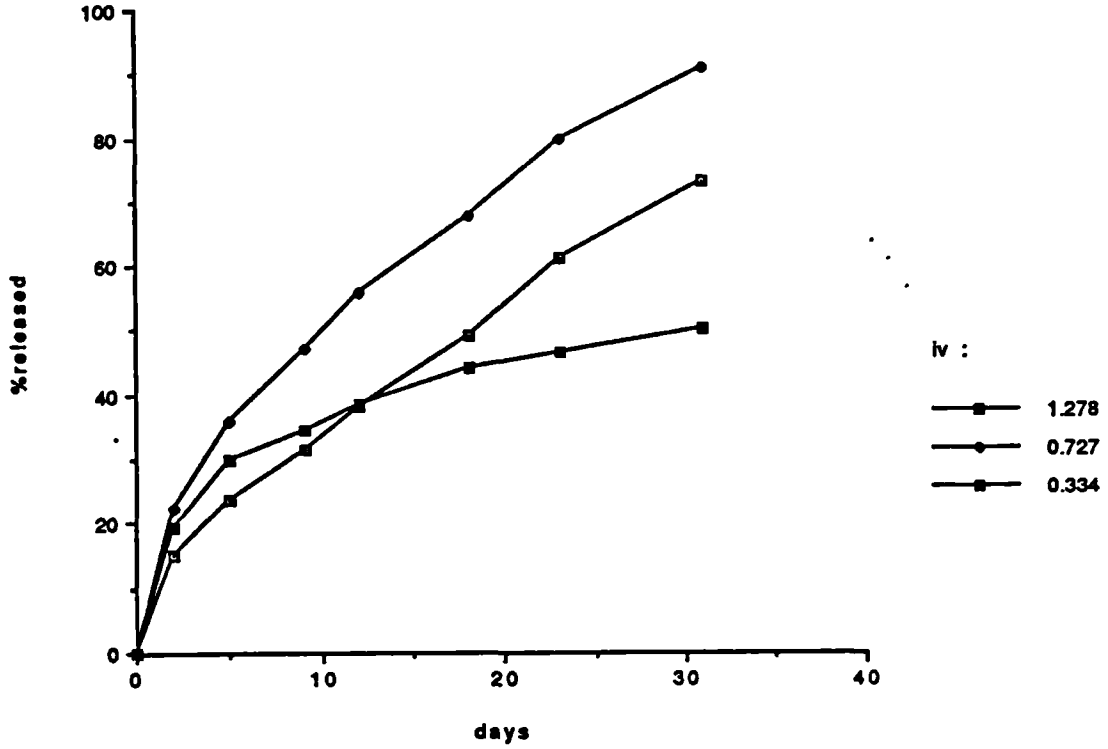


Fig. 48 plots of phenobarbitone release from 85:15(LE:GE % mol) matrices having different mw (dissolution medium: phosphate buffer, pH=7.4, 37°C ; stirring rate: 50 rpm).

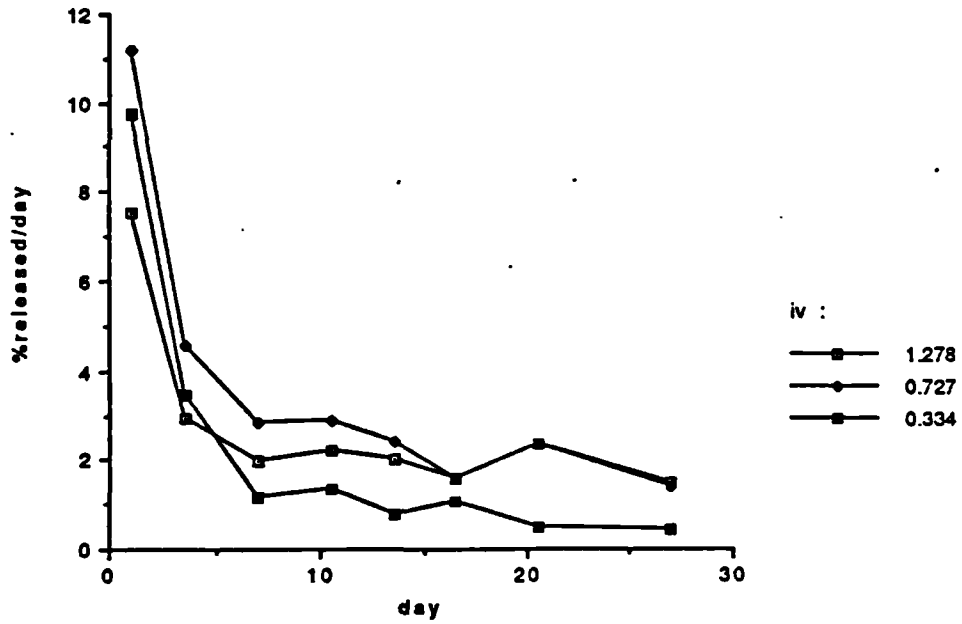


Fig. 49 Rate of phenobarbitone release from 85:15(LE:GE %mol) matrices having differernt mw (dissolution medium: phosphate buffer, pH=7.4, 37°C ; stirring rate: 50 rpm).

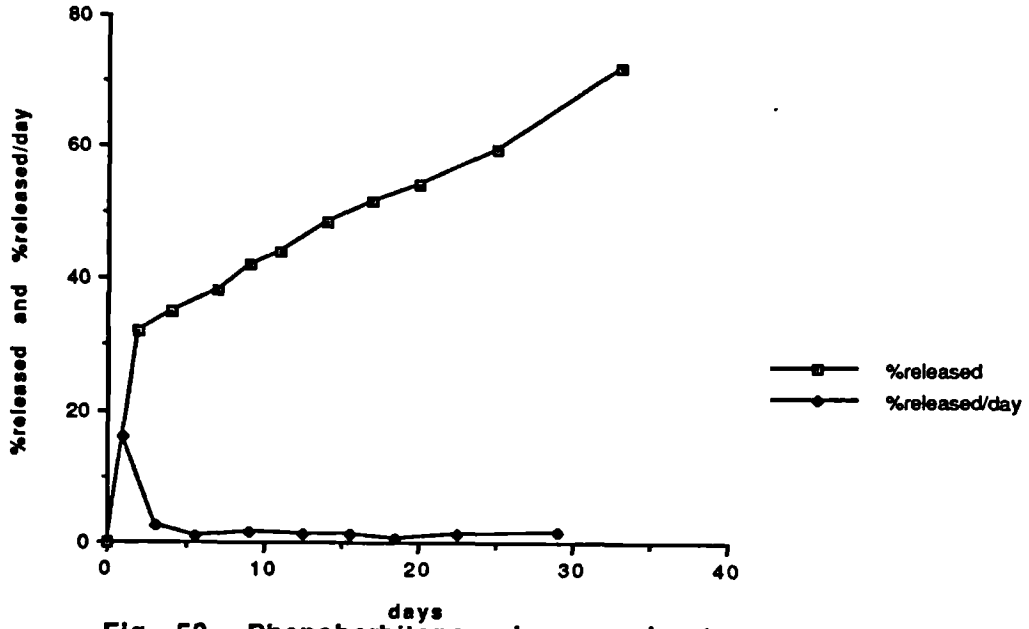


Fig. 50 Phenobarbitone release and rate of release from a 50(0.343) matrix (dissolution medium: phosphate buffer, pH=7.4, 37° C ; stirring rate: 50 rpm).

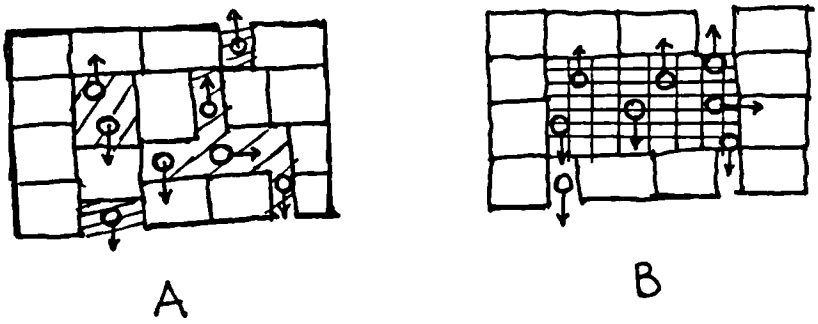


Fig. 51 Drug Release from a Swollen Matrix (A) and from a Matrix with Gelatinized Central Portion (B) (□ polymer particles; o drug molecules).

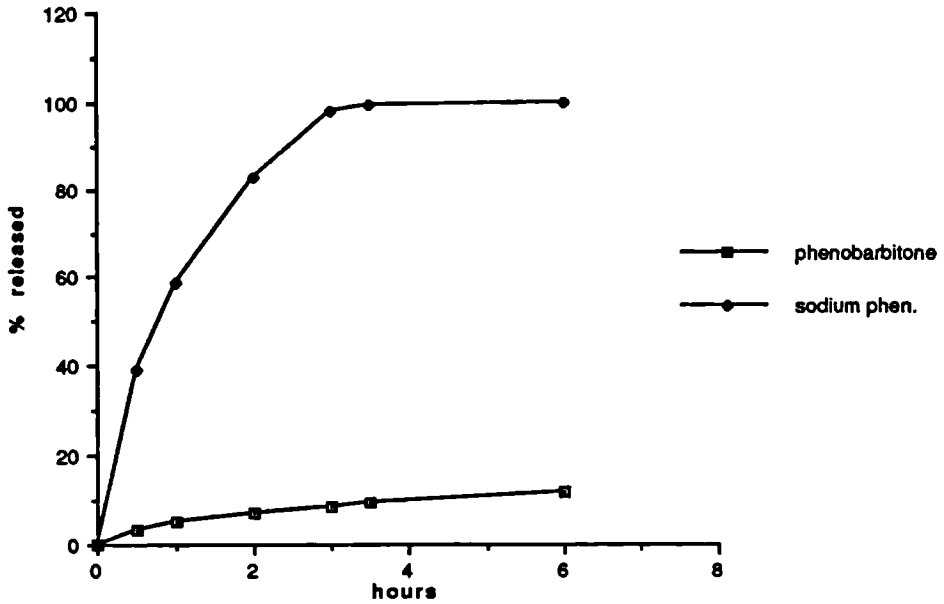


Fig. 52 Phenobarbitone and sodium phenobarbitone release from 75(1.134) matrices prepared by compressing drug-polymer mixtures of 150-250μ at 10 KN (dissolution medium: phosphate buffer, pH=7.4, 37° C ; stirring rate: 50 rpm).

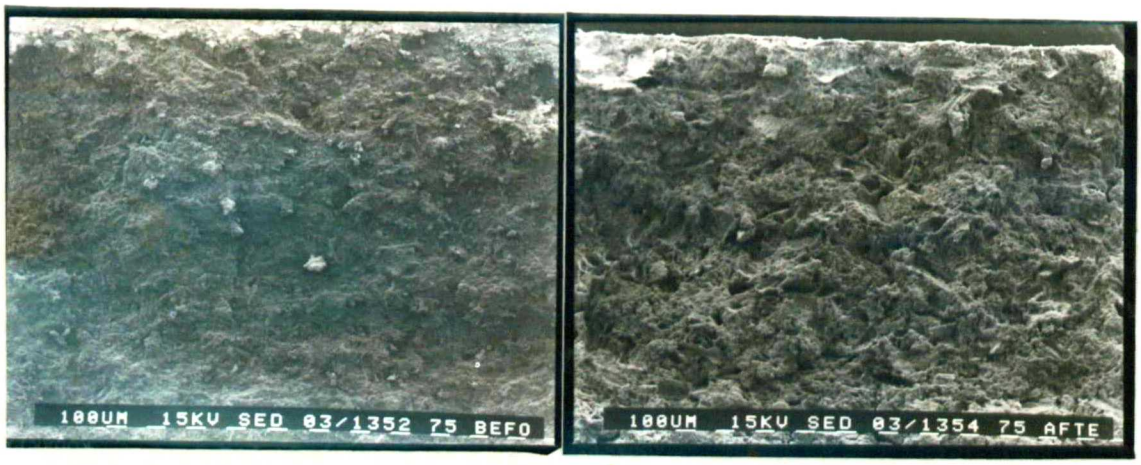


Fig. 53 Scanning Electron Micrographs of 75(1.134) - Phenobarbitone Matrices Before and After 33 Days Dissolution in Phosphate Buffer, pH=7.4

1352: Mid cross-section cut of a tablet before dissolution

1354: Mid cross-section cut of a tablet after dissolution

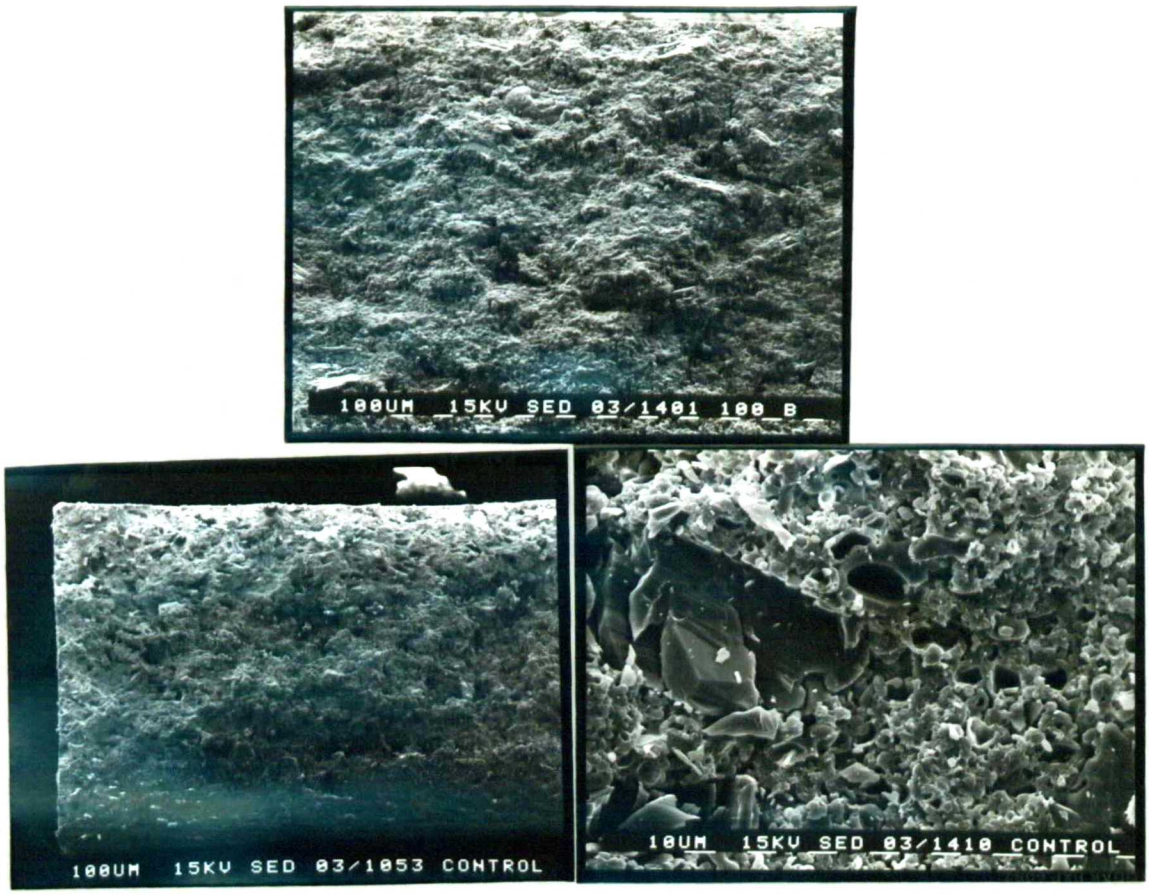


Fig. 54 Scanning Electron Micrographs of 100(1.178) - Phenobarbitone Matrices Before and After 33 Days Dissolution in Phosphate Buffer, pH=7.4

1401: Mid cross-section cut of a tablet before dissolution

1053: Mid cross-section cut of a tablet after dissolution

1410: Detail of the mid cross-section cut shown in 1053.

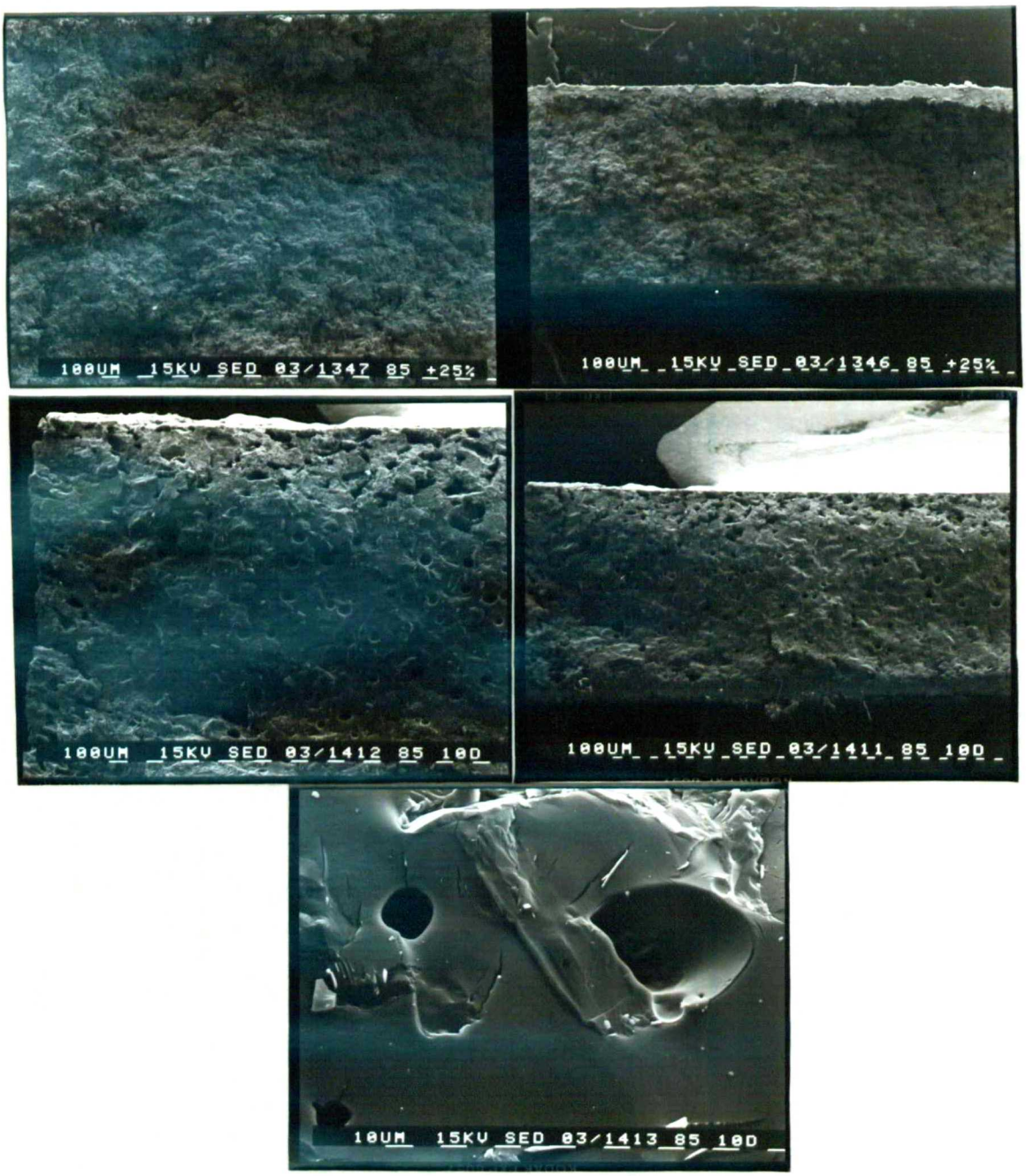


Fig. 55 **Scanning Electron Micrographs of 85(0.308) - Phenobarbitone Matrices (prepared by compressing drug-polymer mixtures of 150-250μ at 10 KN) Before and After Dissolution in Phosphate Buffer, pH=7.4**

1346, 1347: Mid cross-section cut of a tablet before dissolution

1411, 1412: Mid cross-section cut of a tablet after 10 days dissolution

1413: Detail of the mid cross-section cut shown in 1411.

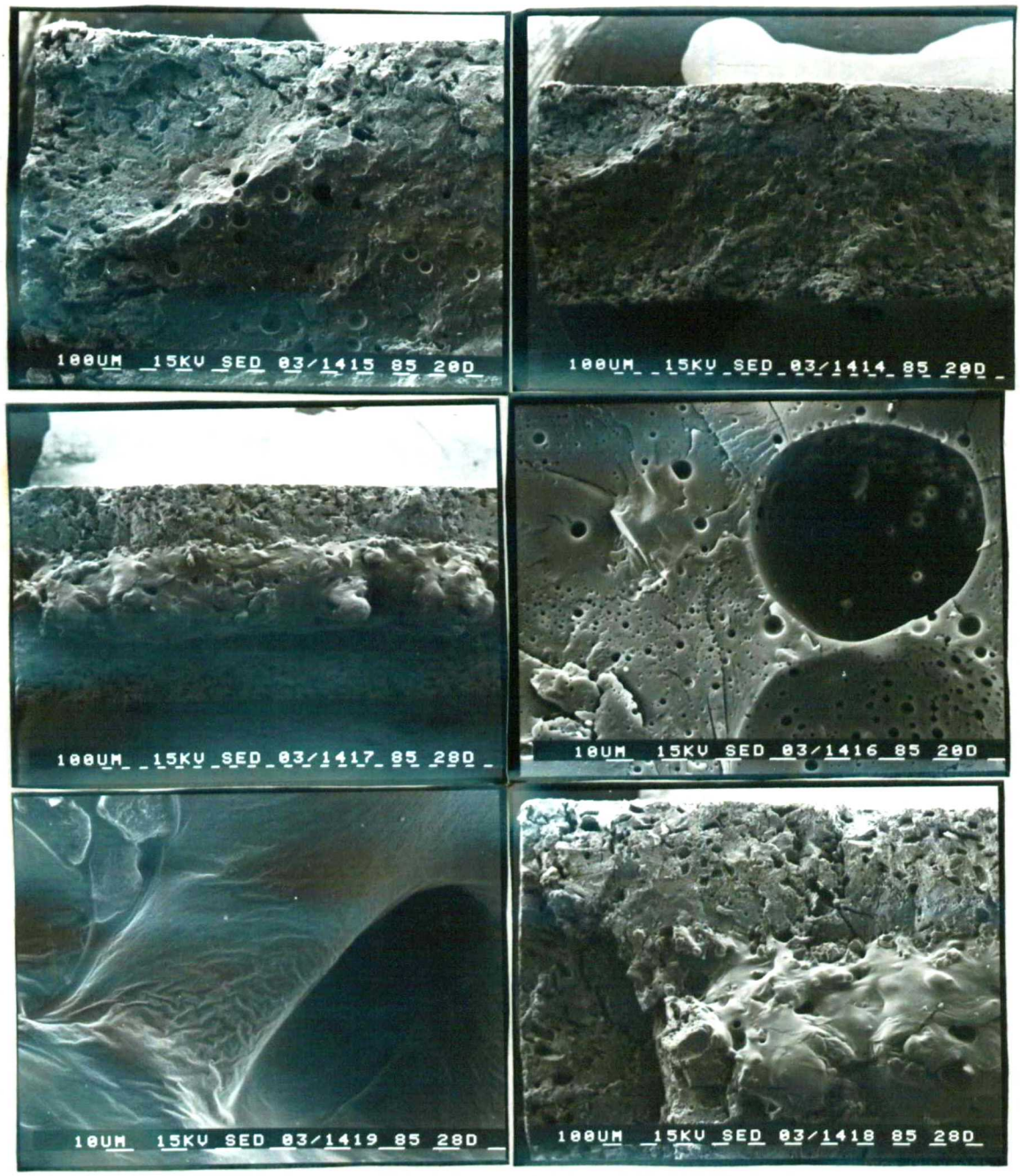


Fig. 56 **Scanning Electron Micrographs of 85(0.308) - Phenobarbitone Matrices (prepared by compressing drug-polymer mixtures of 150-250μ at 10 KN) After Days Dissolution in Phosphate Buffer, pH=7.4**

1414, 1415: Mid cross-section cut of a tablet after 20 days dissolution.

1416: Detail of the mid cross-section shown in 1414. 1

417, 1418: Mid cross-section cut of a tablet after 28 days.

1419: Detail of the mid cross-section cut shown in 1417.

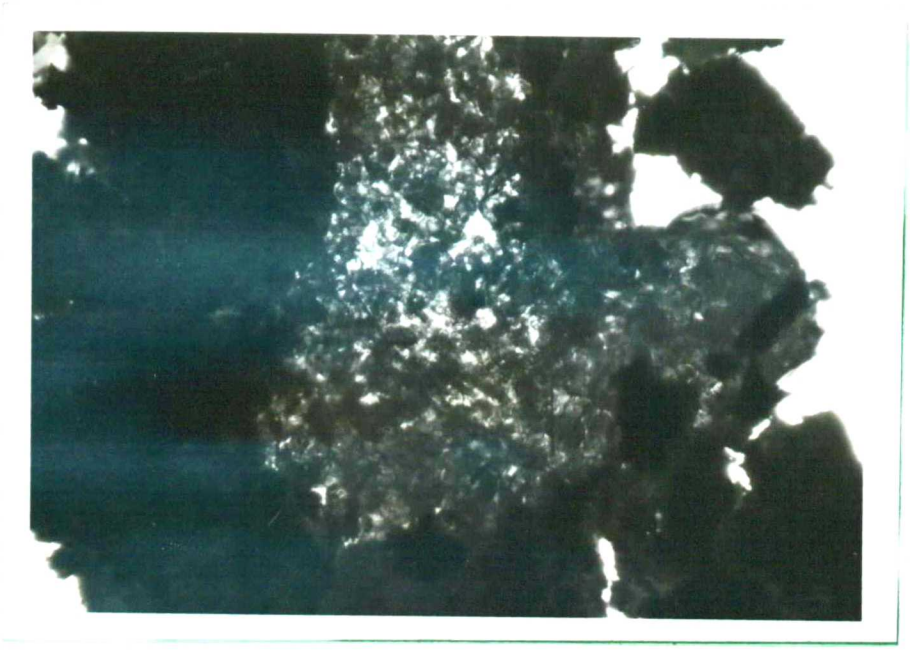


Fig. 57 Photograph of Mid Cross-Section Cut of a 85(0.308) - phenobarbitone Matrix (prepared by compressing drug-polymer mixtures of 150-250μ at 10 KN) After 31 Days Dissolution in Phosphate Buffer, pH=7.4 (Magnification X100).

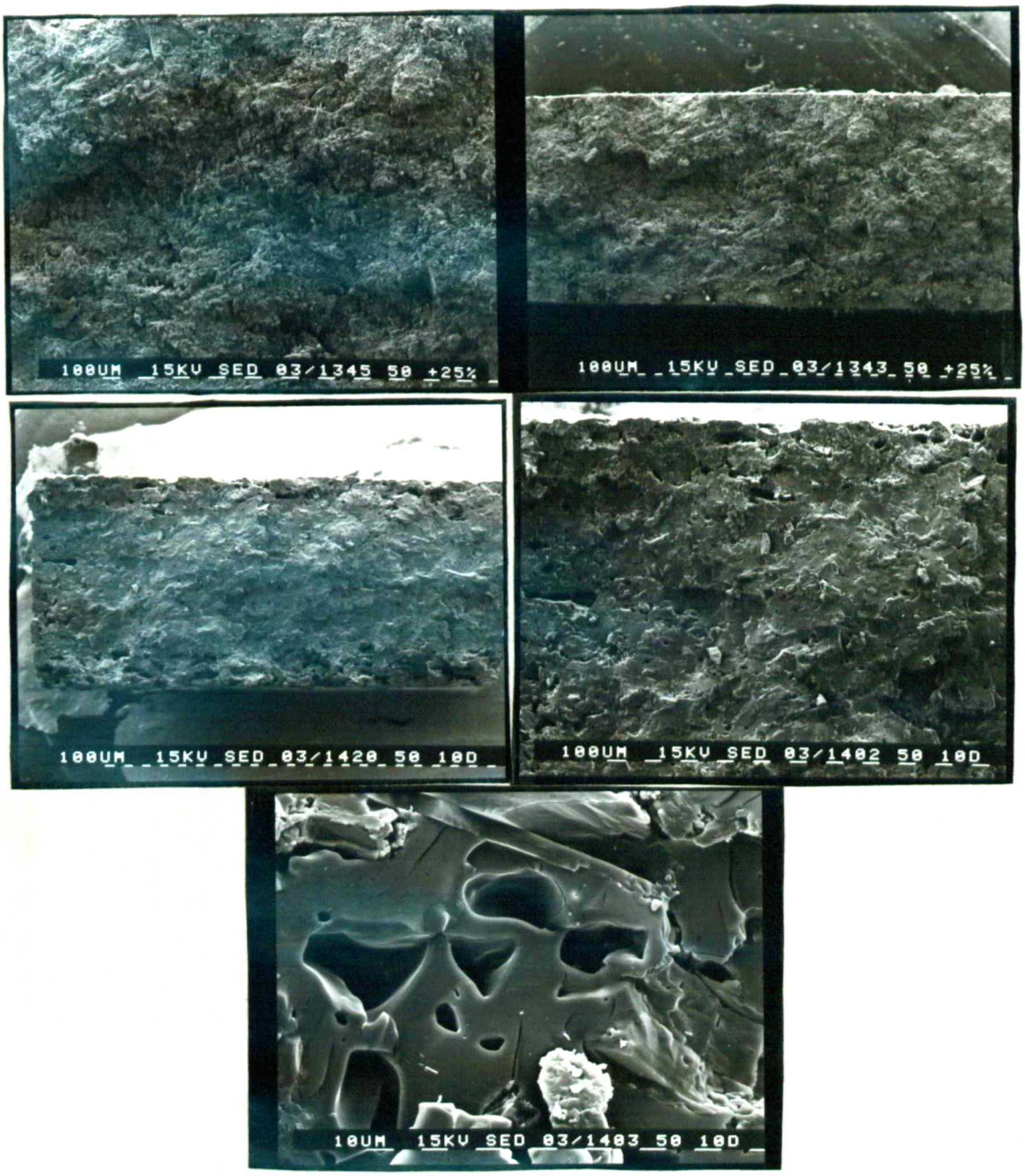


Fig. 58 **Scanning Electron Micrographs of 50(0.343) - Phenobarbitone Matrices (prepared by compressing drug-polymer mixtures of 150-250μ at 10 KN) Before and After Dissolution in Phosphate Buffer, pH=7.4**

1343, 1345: Mid cross-section cut of a tablet before dissolution.

1420, 1402: Mid cross-section cut of a tablet after 10 days dissolution.

1403: Detail of the mid cross-section cut shown in 1420.

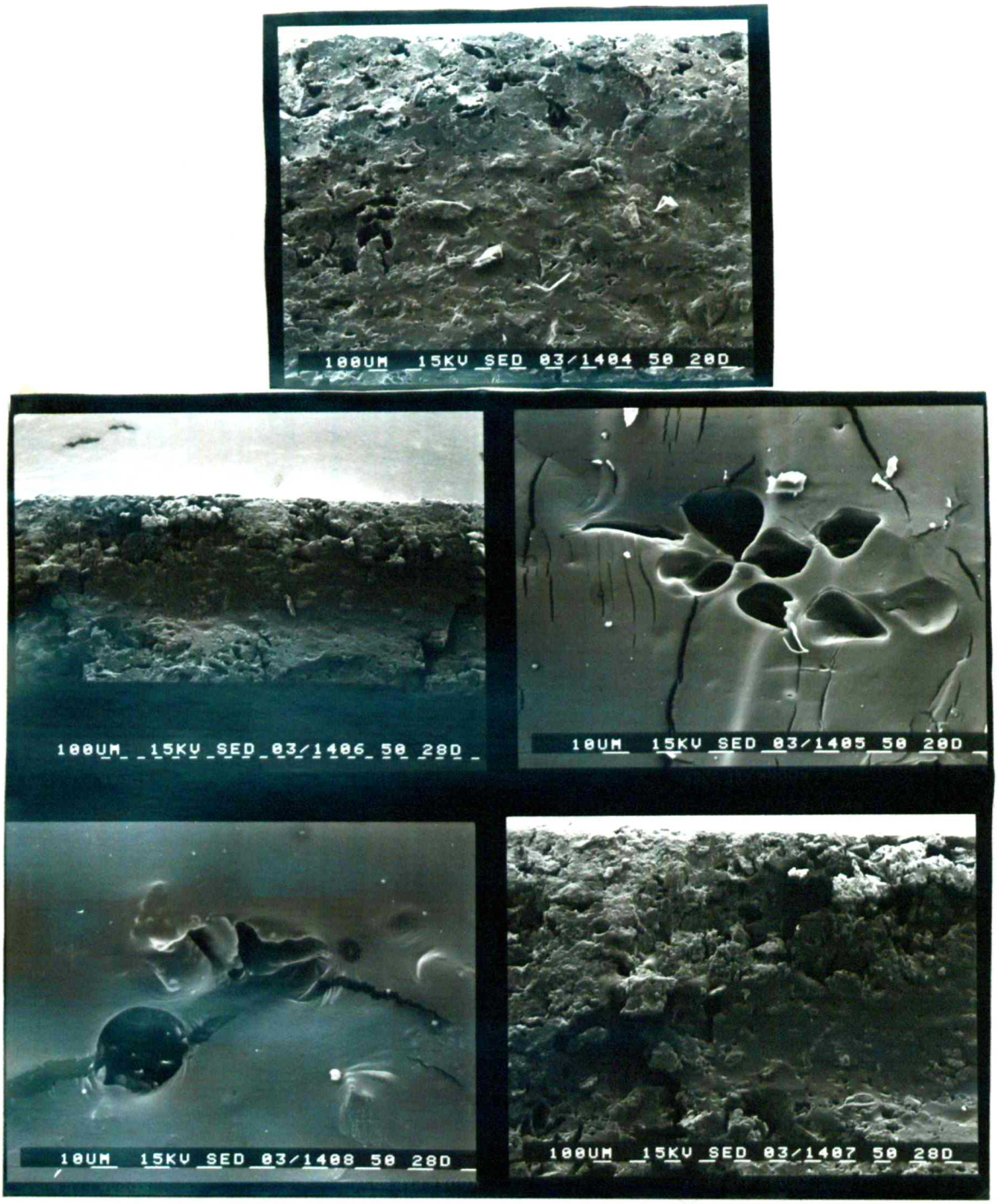


Fig. 59 Scanning Electron Micrographs of 50(0.343) - Phenobarbitone Mixtures (prepared by compressing drug-polymer mixtures of 150-250μ at 10 KN) After Dissolution in Phosphate Buffer, pH=7.4

1404: Mid cross-section cut of a tablet after 20 days dissolution.

1405: Detail of the mid-cross-section cut shown in 1404

1406, 1407: Mid cross-section cut of a tablet after 28 days dissolution.

1408: Detail of the mid cross-section cut shown in 1406 micrograph.

5. GENERAL DISCUSSION

Biodegradable polymers have become increasingly important in the development of controlled release drug delivery systems. The use of biodegradable polymers makes the surgical removal of the depleted device unnecessary, but perhaps most importantly, the degradation of the carrier can be utilized to control the rate of drug release. A number of biodegradable polymers are currently being evaluated as carriers for sustained drug delivery, but the polymers receiving the most attention at this time are the homo-and-copolymers of lactic and glycolic acid. This is mainly because of their established biocompatability and regulatory approval of their application as biodegradable surgical sutures.

Low molecular weight poly(lactic-co-glycolic) polymers can be prepared by the direct condensation of lactic and glycolic acids in aqueous solutions. With this method poly lactic acids of relatively high mw's were obtained by removing the water with an entraining agent in the presence of mineral acid catalyst. The polymers of moderate mw were viscous oils, whereas those having molecular weights of approximately 3,000 and above were brittle glasslike masses (Fillachione and Fischer, 1944). High mw polymers (mw > 10,000) cannot be produced by this method because a high degree of dehydration (>99%) would be required, which is difficult to achieve because Henry's law considerations make it difficult to distil the infinitesimal quantity of water in equilibrium with a polymer of this mw.

High mw (>10,000) poly(lactide-co-glycolide) polymers can be prepared by the ring opening polymerization of the cyclic "monomers" lactide and glycolide. This ring opening polymerization proceeds through the pair addition of lactic or glycolic acid units yielding polydimers. When protic or Lewis acids are used the mechanism of polymerization is cationic, whilst a co-ordinate mechanism has been proposed when organometallic catalysts are used (Cherdron *et al.*, 1962; Dittrich and Schulz, 1971).

Although the importance of polymerization conditions on the properties of the resulting polymers has been recognised the effects of changing the polymerization conditions have been studied in a rather empirical manner, leading frequently to contradictory findings. In this work the synthesis of poly(lactide-co-glycolide) by the ring opening polymerization of lactide and glycolide has been thoroughly investigated from a pharmaceutical viewpoint. The effects of changing the polymerization conditions were discussed with respect to the mechanism of polymerization. The effects of preparative variables on the yield of polymerization were also considered since a satisfactory yield is required to make polymer synthesis cost effective.

Exclusion of moisture during lactide/glycolide preparation and storage, as well as during polymerization, is essential if high mw polymers are to be obtained. It was found that small lactide/glycolide crystals having a higher specific surface area absorbed moisture at a higher rate during handling and storage and resulted in lower mw polymers than

larger crystals. Moisture absorbed by the monomers caused their hydrolysis to acidic products, which act as chain transfer agents, terminating the polymerization. The α form of glycolide, which is more stable hydrolytically, is slowly converted to the β isomer on standing at ambient temperature (Frazza and Schmitt, 1971). Therefore, the monomers should preferably be used immediately after their preparation or they should be effectively protected from moisture during storage. Because moisture causes monomer hydrolysis, but also functions as chain transfer agent itself, the polymerization should be carried out in an inert atmosphere or in highly evacuated vessels.

Two type of catalysts, which have been reported to be particularly effective in the polymerization of lactide/glycolide are Lewis acids and organometallic compounds. The comparative effectiveness of these catalysts was investigated by using antimony trifluoride as representative of the first type and stannous octoate as representative of the second. Stannous octoate was preferred over diethyl zinc or trialkyl aluminium, which have also been used (Wise *et al.*, 1979a), because the last two compounds are pyrophoric, igniting on contact with air, which makes their handling difficult. Furthermore, stannous octoate had been approved by the FDA (Food and Drug Administration, USA) as a food stabilizer so that possible residual catalyst in the polymers would not represent a serious problem. Under both polymerization conditions used, stannous octoate was far more effective, resulting in polymers having 3 to 9 times greater inherent

viscosity than polymers synthesized using antimony trifluoride (Table 3). This indicates that organometallic compounds are more effective catalysts than Lewis acids for the polymerization of lactide/glycolide. Since stannous octoate was found to be more effective, this catalyst was selected for the remainder of the work.

The effect of catalyst level on the mw of the resulting polymer and on the yield of polymerization was investigated at two temperatures, one high (190^{o}C) and one low (130^{o}C). At both temperatures the mw and the yield passed through a maximum at fairly low catalyst levels, before falling at higher catalyst concentrations. The amount of catalyst required for polymers with high mw appeared to coincide with that resulting in a high yield (Figs. 12 and 13, Table 4). From the reaction of catalyst with monomer active species are formed (Species A in reaction shown in Fig. 11) which initiate the polymerization. The rate of polymerization increased with an increase in catalyst concentration (Table 6) due to increased rate of initiating species generation. Thus, increasing the catalyst concentration resulted in an increase in both polymer mw and yield of the polymerization. However, excessive increase in catalyst levels caused a too high rate of polymerization, resulting in a sudden mw build up followed by a mw decline due to depolymerization reactions. Depolymerization probably takes place through a "back biting" mechanism in which an active centre in a polymer molecule attacks a carbonyl group in the same molecule, instead of a monomer carbonyl group, resulting in the

cleavage of the polymer chain into two segments (Fig. 14). The probability of these "back biting" reactions increases with an increase in the catalyst to monomer ratio, accounting for the mw decline when catalyst levels beyond the optimum for a given set of polymerization conditions were introduced in the polymerization mixture.

Polymers of higher mw were obtained at lower temperatures (Figs. 12 and 13). This is attributable to the increased probability of "back biting" depolymerization reactions because rotational and folding mobility is enhanced at higher temperatures.

The polymers exhibited similar polymerization behaviour, with regard to the polymerization conditions, irrespective of their composition. Thus, the mw of both 90:10 and 70:30 (LE:GE w/w in the starting polymerization mixture) compositions followed the same pattern of change with respect to catalyst level. The catalyst level resulting in polymers with the highest mw (optimum catalyst level) was the same for both compositions. However, the compositions rich in glycolide appear to require more severe polymerization conditions, since, at all catalyst levels, polymers produced from the 90:10 starting composition had a higher mw than those prepared from the 70:30 starting composition. An increase in the amount of catalyst above the optimum, for a given set of polymerization conditions, did not result in higher mw polymers, indicating that the polymerization of mixtures with high glycolide contents

probably requires higher polymerization temperatures (Figs. 12 and 13).

When polymerization proceeds through chain reactions polymer of high mw is normally formed at once and polymer mw changes little throughout the polymerization. The mw of the polymers synthesized here continued to increase throughout the polymerization (up to 4 hours when optimum catalyst levels were used), even at conversions higher than 90% (Fig. 18), indicating that poly(lactide-co-glycolide) polymerization is not a chain reaction in the kinetic sense. The effect of polymerization time appears to depend on the amount of catalyst used. At optimum catalyst levels the yield remained essentially constant, but the mw fell at polymerization times longer than 4 hours (Figs. 16 and 17). As the high yields obtained with a 4 hours polymerization indicated, the polymerization had been essentially completed within the 4 hours period, so that only "back biting" reactions could occur after that period causing depolymerization. Using a sub-optimum catalyst level, lower mw and yield were obtained, which were still increasing at periods longer than 4 hours (Figs. 16 and 17).

The time of polymerization was found to affect the composition of the resulting polymers. Glycolide, being more reactive, was preferentially polymerized in the initial stages, so that polymers prepared using short polymerization times were richer in glycolic acid units than those prepared using longer polymerization times

(Table 7). These results indicate that when optimum amounts of catalyst for a given temperature are used, 4 hours polymerization should be carried out, since polymers of lower molecular weights at a lower yield are produced using shorter polymerization periods, whilst the polymer mw falls at longer periods. Furthermore, the composition of polymers appears to stabilize after 4 hours polymerization (Table 7), so that polymers with consistent properties can be prepared using a 4 hours polymerization period. When sub-optimum catalyst levels are used longer polymerization times are required, whilst with higher than the optimum catalyst levels the reaction proceeds to rapidly and shorter polymerization times have to be employed to obtain the same degree of polymerization.

The polymerization of lactide/glycolide in the presence of small amounts of alcohol, such as lauryl alcohol has been proposed to be cationic (Frazza and Schmitt, 1971). It is believed that in polymerizations proceeding through a cationic mechanism the catalyst reacts with a co-catalyst to form the initiating species. When lauryl alcohol was included in the polymerization mixture as a co-catalyst, increasing the lauryl alcohol concentration caused both a decrease in the mw of the resulting polymers and in the yield of polymerization (Table 5). This was attributed to the interruption of the proton exchange between the polymer chains and the monomers, which is responsible for chain growth, by the lauryl alcohol molecules.

Polymers synthesized in this work having an inherent viscosity of approximately 0.2 or less were yellowish, granular, brittle materials, whereas higher mw polymers were tough fibrous materials which could not be powdered by grinding. Therefore alternative methods of producing these polymers in powdered form had to be developed. For this purpose the spray drying technique was adopted.

The microstructure of biodegradable polymers can be investigated by NMR spectroscopy or by degradation experiments. In the first method the ^{13}C - NMR spectrum of the sample is recorded and its fine structure could provide information for the monomer sequence in the polymer molecules. In the second method the sample is allowed to degrade in an aqueous environment and the ratio of lactic to glycolic acid units is determined periodically. If there is a large amount of block copolymer in the sample, the ratio of lactic acid to glycolic acid units increases with time, since the glycolic acid sequences are preferentially hydrolyzed. In this work the first method, which is more rapid and possibly more sensitive, was adopted.

The structure of the ^{13}C - NMR spectra indicated that block copolymers were produced, irrespective of polymer conditions, due probably to the higher reactivity of glycolide monomer. The block nature of the polymers was also indicated by the presence of insoluble material in tetrahydrofuran or chloroform material from polymers rich in glycolide, such as the 50:50 (LE:GE %mol) polymers. The

insoluble material was probably polymer molecules having large blocks of glycolic acid units, since poly(glycolide) is insoluble in common organic solvents. A random monomer sequence would be preferred because random copolymers would exhibit more reproducible behaviour, such as solubility in organic solvents and biodegradation rate, consistent with their composition and molecular weight. Copolymers with a narrow range of chain composition may possibly be made using a monomer feed technique (Askill and Gilding, 1981). However, the need for accurate metering of a high temperature lactide and glycolide mixture, together with the rapidity of polymerization, makes this prospect very difficult experimentally.

Because racemic lactide was used to synthesize the polymers all samples examined were amorphous, showing a Tg which increased with increasing lactide content, or mw of the polymer (Table 8). This might have a significant effect on the polymer performance as a controlled drug release excipient. The increase in the degradation rate of spray dried polymer powders with an increase in glycolide content, or a decrease in polymer mw (Figs. 27, 30 and 33), was attributed, amongst other factors, to a reduction of Tg. This caused an increase in both the water penetration rate and the ease with which the transition state for ester hydrolysis could be achieved.

The results obtained from the investigation of poly(lactide-co-glycolide) synthesis show that the polymerization conditions affect the mw and composition of

the polymers formed and, consequently, all polymer properties which depend on polymer mw and composition. There is a significant interdependence between such preparative variables as the amount of catalyst, time and temperature so that the effect of changing any one of them on the properties of the resulting polymer depends on the level of the other two. It appears possible to control the properties of the polymers formed by judicious adjustment of the polymerization conditions. Thus, the mw of the resulting polymers can be decreased by employing lower than optimum catalyst concentrations, by decreasing the polymerization time, by incorporating small amounts of alcohol in the polymerization mixture, or by a combination of those. The mw of the polymer can also be decreased by fractionization, but the low yields obtained with this method [less than 50% according to Kitchell and Wise (1985)] make fractionization non cost-effective. In general it is advantageous to prepare a polymer with the desired properties in the first place rather than to modify the properties of an already produced polymer.

Larger quantities of polymers, with different compositions and mw's, were synthesized by modification of the preparative procedure based on the data acquired in the study of polymer synthesis. These polymers were spray dried from chloroform solution using a mini spray dryer. The main problem encountered was the production of threads, instead of particles, when relatively high mw polymers were sprayed, unless very dilute solutions were used. This was attributed to the nature of poly(lactide-co-glycolide)

molecules and the strong intermolecular interactions of both physical and chemical nature. Very dilute (1-2% w/v) solutions of the high mw polymers had to be used in order for polymer particles to be obtained. There was also a significant deposition of partially dried material on the wall of the drying chamber, which was attributable to the tacky nature of the polymers at the drying temperature and to the characteristics, such as the size and atomizing method, of the spray dryer used. It was, therefore, necessary to recycle the deposited material twice in order that acceptable spray drying yields (70 - 80%) be achieved. The use of very dilute solutions and the need for deposit recycling increased the time and cost of spray drying per polymer batch. The use of larger spray driers, with more efficient atomizing equipment, may improve the spray drying characteristics of poly(lactide-co-glycolide) polymers. The spray dried particles appeared to be porous, approximately spherical agglomerates of tiny spheres probably produced as droplets attached to each other during spray drying. Because of their almost spherical shape and their sufficiently high particle density (around 1.3 $g.cm^{-3}$) significant problems with regard to powder flowability are not expected, although the smaller particle sizes, 63-149μ, and especially 45-63μ, showed a certain degree of cohesiveness. The agglomerate and rather loose texture of the particles probably increased powder compressibility. Soft and ductile powders were obtained by spray drying the polymers. The yield pressure values obtained were in the range of 28-33 MPa, and depended on the compaction rate, indicating a material consolidating through plastic

deformation. The characteristics of the polymer, such as mw and composition, did not appear to have any significant effect on the yield pressure of the powders (Table 13).

Degradation of poly(lactide-co-glycolide) polymers involves bulk hydrolysis of ester bonds, resulting in a reduction in polymer mw with time and dissolution of the small chain fragments formed, which in turn results in time dependent mass loss from the polymer. The polymer hydrolysis is usually followed by measuring the decrease in polymer mw, however, it was shown that the rate of hydrolysis does not always coincide with the rate of mw reduction. The dissolution of small oligomers may cause an apparent increase in the mw of the remaining polymer and create a false picture of the polymer hydrolysis (Fig. 27). The rate of mw reduction may be considered to safely reflect the rate of polymer hydrolysis only before mass loss from the polymer takes place.

Pitt *et al.* ($1981_{a,b}$) proposed that the hydrolysis of poly(ϵ-caprolactone) and related polyesters is autocatalyzed by the carboxylic acid end groups generated. However, for polymers in powder form the surface hydrolysis reactions will be significant. These surface reactions will be controlled by the properties of the incubation medium and in slightly alkaline solutions of pH = 7.4 the acidic degradation products will be converted to neutral salts. It would appear reasonable to expect that autocatalyzed hydrolysis in such media would be negligible. Rate equations were developed for autocatalyzed either by

the dissociated or dissociated form of the carboxylic end groups, and also non-autocatalyzed polymer hydrolysis. The degradation data fitted best equations describing non-autocatalyzed hydrolysis indicating that the hydrolysis of poly(lactide-co-glycolide) in buffer, pH = 7.4, followed such a mechanism (Table 12).

The rate of polymer hydrolysis increased with respect to the glycolide content, which was attributed to the greater susceptibility of the glycolate ester bond to hydrolysis as well as to the decrease in the Tg of the polymer with increasing glycolide content (Figs. 27 and 29). A decrease in polymer mw caused an increase in the polymer hydrolysis rate because of the increase in density of the hydrophillic chain end groups and the decrease in polymer Tg (Figs. 30 and 33). The rate of mass loss from the polymer also increased with increased glycolide content, or a decrease in polymer mw, because of the increased rate of polymer hydrolysis.

The mass degradation profiles had sigmoidal shape consisting of three distinctive regions: an initial lag time corresponding to the time required for the production of small soluble chain fragments through chain scission, an apparent steady-state mass loss region, during which the mass loss rate appears to be constant, and finally a late region where the mass loss rate diminishes as the polymer rate is exhausted (Figs. 29 and 31).

Based on the characteristics of mass degradation profiles the lag period was determined as the time required for an apparent steady-state mass loss to be established. Accordingly, the lag period can be determined graphically as the time of the first inflection in the percent polymer mass remaining versus time plots. If the point of inflection in the curve is not clear, as in the case of polymers having low mw or high glycolide content (Figs. 28 and 31), the lag period can be determined by fitting the data of the steady-state mass loss region to the zero order rate law and calculating the time for which the percent remaining polymer mass becomes equal to 100 in the resulting regression equations (Equations 13 and 14). Unlike the method proposed by Schindler *et al.* (1977), in which the lag period is defined as the time required for 5% mass loss to occur, the method proposed in this work has physical significance, because the lag period is recognised as the period required for a composite phenomenon to reach "equilibrium". Furthermore, lag period values determined according to this method are based on the actual degradation data of the individual polymer. The lag period was found to increase with an increase in lactide content, because polymer hydrolysis rate falls with increasing lactide content, or with an increase in polymer MW, because polymer hydrolysis rate falls with increasing polymer MW, but also because longer times are required for a polymer molecule to be reduced to small soluble oligomers as the polymer mw increases (Figs. 29 and 34, Table 11).

An increase in the particle size of the polymer powder, sample 50(0.443), caused a significant decrease in both the hydrolysis rate and the mass loss rate (Table 10). The decrease in hydrolysis rate was attributed to the decreased contribution of the surface hydrolysis, because of the lower specific surface area, and to the delay in the establishment of the polymer bulk "equilibrium" hydrolysis rate. The latter was considered to be responsible for the lag period observed in the iv versus time profile of the 50(0.443) sample, which was the only case lag period was observed in the iv versus time profile (Fig. 30). The decrease in mass loss rate was attributed to the decreased initial hydrolysis rate and to the increased difficulty and time required for the removal of soluble chain fragments from the larger particles. These results indicate that the degradation rate of poly(lactide-co-glycolide) is affected by the specific surface area of the polymer form.

When the effects of composition and mw on polymer degradation rate were quantitatively compared it was found that composition is a more dominant factor than mw in poly(lactide-co-glycolide) degradation (Figs. 35 and 36). The results obtained in this study would indicate that the composition of the polymer determines an average value around which the degradation time fluctuates as a result of modifications in polymer mw. The degradation times of polymers with small differences in composition can overlap as a result of differences in mw, but the degradation times cannot overlap when big differences in composition are involved, irrespective of the mw of the polymers.

Drug release from heterogeneous matrices occurring by drug diffusion through liquid filled capillaries and pores will depend on the ability of the dissolution medium to wet the polymer surface. The wettability of spray dried poly(lactide-co-glycolide) powders was assessed by conducting contact angle measurements. The h-ϵ method was used to determine the contact angle between a polymer compact and water (Lee *et al.*, 1976). The contact angle values obtained were in the range 72^{o} - 78^{o} (Table 14), indicating a moderate polymer hydrophobicity. They also indicated that the water will penetrate into the capillaries and pores of matrices prepared by compressing poly(lactide-co-glycolide) polymers. The mw of the polymer did not appear to have any effect on the contact angle values, whereas an increase in glycolide content tended to lower the contact angle, reflecting the increased polymer hydrophilicity as its content in hydrophobic lactic acid units is reduced. However, the decrease in contact angle with polymer content in glycolide was not statistically significant (Table 15).

The polymer hydrophilicity can also be assessed by measuring the water uptake by the polymer. This will determine the volume of the aqueous regions in the polymer through which drug diffusion can take place which in turn affects the rate of drug release. Furthermore, it will affect the degradation rate of the biodegradable polymers, because hydrolysis rate depends on water availability.

Water uptake by poly(lactide-co-glycolide) matrices increased steadily as matrix hydrophilicity increased with time due to polymer degradation. The increase in hydrophilicity was due to the generation of hydrophillic hydroxyl and carboxylic acid end groups through ester bond hydrolysis. Water can also be drawn into the matrix through an osmotic mechanism. The oligomers produced in the tablet interior diffuse out from the matrix at a lower rate than those produced in the surface region of the tablet and cause an osmotic pressure difference between the bulk solution and the solution within the tablet to be established. Advanced degradation transformed the interior of the tablet into a hydrogel (Figs. 56 and 57). This had a significant effect on the rate of drug release from matrix tablets as drug in the central portion of the tablets had to diffuse through this gel to be liberated. Thus, water was drawn continuously into the matrix, increasing the matrix weight with time, but when mass loss due to degradation outweighed the gain from water absorption the weight loss of the matrix began to fall. (Fig. 38)

An increase in glycolide content or a decrease in polymer mw caused an increase in both the percent water uptake and water uptake rate due to the increased rate of polymer hydrolysis and decreased Tg values (Figs. 38 and 39).

An "equilibrium water uptake" was defined which represented the percent water uptake at the point of the initial part of the water uptake versus time plot where the water uptake

rate became minimum. The "equilibrium" value may be considered to express the inherent hydrophilicity of the original polymer, as negligible degradation occurs during the first few days by which time the "equilibrium has been reached. Both the water uptake rate until "equilibrium" and percent water uptake at "equilibrium" increased with increasing glycolide content or decreasing polymer mw (Figs 38 and 39, Table 17).

The swelling (% increase in matrix thickness) of the matrix after 25 days immersion in phosphate buffer, pH = 7.4, increased with increasing glycolide content, or decreasing mw of the polymer (Table 18). This was attributed to the increased polymer affinity for water as polymer hydrophilicity increases, as well as to the decreased Tg values of the polymers. The polymers swell considerably, although they absorbed only small quantities of water. For example, poly(lactide), sample 100(1.178), absorbed only 1.67% water but swelled 18.31% (Table 18). A possible explanation might be the plasticization of the polymer caused by the absorbed water, which would enhance the expansion of the polymer molecules and would increase the free volume in the polymer. Pitt and Gu (1987) observed that water uptake from a 70:30 (l-LE:GE %mol) polymer caused a decrease in the polymer Tg which was attributed to the plasticization of the polymer by the absorbed water.

The contact angle with water values appeared to be less sensitive to changes in polymer characteristics than the water uptake values. As an equilibrium contact angle was

measured with the h-ϵ method employed in this work, it might be possible that polymer chains lying on the surface of the compact reoriented themselves, allowing contact by water molecules to the most hydrophillic polymer portion, such as chain segments consisting of block of glycolic acid units, in order to produce the lowest possible interfacial free energy. The reordering of the surface has been used to explain the decrease in contact angle values with time (dynamic effects) in polymer systems (Buckton, 1990). Reorientation of the surface chains would reduce the differences in hydrophobicity between the polymers and would account for the relative insensitivity of contact angle to the polymer characteristics. On the other hand the effect of polymer Tg probably supplement the effect of polymer hydrophilicity on water uptake, increasing the influence of polymer properties on water uptake.

Mixtures of spray dried poly(lactide-co-glycolide) polymers and phenobarbitone were compacted to prepare matrix tablets. The effects of technological factors were investigated with short release experiments *in vitro*. The main concern was to find out how the change of technological factors would affect the rate of initial drug release and to identify the conditions producing satisfactory low initial drug release for a prospective sustained release dosage form.

It was found that an increase in compaction pressure caused a decrease in the rate of drug release attributable to the decreased porosity of the matrix (Table 19). The effects

of compaction pressure appeared to depend on the particle size of the drug-polymer mixture used, being more pronounced with the large particle size function (Figs. 42 and 43). Small particles are probably capable of higher densification through interparticulate slippage and rearrangement than large particles, therefore they form dense compacts at relatively low compaction pressures and little further densification is achieved by increasing the pressure beyond a certain value. Thus, the porosity of the tablets prepared from small particles (45 - 63μ) did not decrease significantly at compaction forces higher than 5 KN (Table 19), accounting for the small difference in drug release rate between the tablets prepared using compaction forces higher than 5 KN. Sufficient mechanical strength is a prerequisite for sustained release matrix tablets. The diametral breaking test (Fell and Newton, 1970) was used to determine the tensile strength of poly(lactide-co-glycolide) matrix tablets. Tablets of high tensile strength were obtained even at low compression due to the high plasticity of the spray dried polymers (Table 20). An increase in the particle size of the drug-polymer mixture had a relatively small increasing effect on drug release rate, probably due to the high plasticity of the spray dried particles which diminish the influence of particle size on the properties of the tablets produced (Fig. 44). By contrast an increase in the drug proportion in the matrix caused a significant increase in the rate of drug release (Fig. 45).

These results indicated that the rate of drug release can be affected by changes in formulation factors. When powders having a particle size range lower than 250 - 420μ were compressed using compaction forces higher than 5 KN the resulting tablets released less than 30% of their drug content in 2 days, which may be regarded as providing a prospective sustained release formulation. Therefore, drug-polymer mixtures of 150 - 250μ particle size range, which appeared to have better flow properties than the smaller particle sizes, were compacted at 10 KN to produce tablets for the investigation of the effects of polymer properties on drug release conducting relatively long experiments *in vitro*.

It was found that the release of phenobarbitone was significantly sustained, the amount of drug released over a 33 day period ranging from 50 to 97% (Figs. 46, 48 and 50), indicating the suitability of using matrix tablets prepared with spray dried poly(lactide-co-glycolide) polymers in long-term controlled drug delivery.

Drug release profiles consisted of three regions. An initial region of comparatively high release rate, which was attributed to the rapid leaching of drug from the surface or close to the surface of the tablet (burst release stage). This was followed by a region of lower and essentially constant release rate (steady-state release region). In the concluding stages of the release the rate decreased as exhaustion of drug in the matrix approached (final release region) (Figs. 46 and 48).

The existence of a long steady-state release region, which represented a high proportion of the overall release profile extending approximately from the time required for 20% to the time required for 80% drug release to take place, indicated that the release did not follow the Higuchi matrix release kinetics (Higuchi, 1963). A composite mechanism of drug release was proposed involving diffusion of the drug through water filled capillaries and pores of the matrix and drug diffusion through the swollen polymer (Fig. 51). The significant delay in drug liberation was attributed to the decreased drug diffusion rate through the swollen polymer as compared to that through water and to the decreased drug diffusion rate via water filled pores due to the pore volume reduction caused by polymer swelling. The constant drug release rate over the steady-state stage of release is complex and may be attributed to a number of factors including polymer degradation and water uptake. These could cause a progressive increase in drug release rate which would compensate for and balance the decrease in release rate caused by the increasing drug diffusion path with time.

The rate of drug release increased with an increase in the glycolide content of relatively high mw polymers. This was attributed to the increase in water uptake and swelling, which enhanced drug diffusion through the polymer. This was further aided by the increase in polymer degradation rate which resulted in an increased rate of aqueous channel generation within the polymer through which diffusion and drug release could take place. The steady state release

from a 75:25 poly(lactide-co-glycolide) was found to be 3 times greater than that from a poly(lactide) polymer (Table 21).

The effect of polymer mw on the rate of drug release was not as straight forward as with polymer composition. Decreasing the mw initially caused and increase in the drug release rate due to the increased swelling, water uptake, and degradation rate, but further decrease in mw caused the opposite effect (Figs. 48 and 49). This was attributed to the rapid hydrolysis of the low mw polymer which caused the gradual but rapid transformation of the central portion of the tablet to a hydrogel. This allowed diffusion through the gel as the only release pathway for drug in the tablet interior, eliminating release by diffusion through aqueous channels. Thus, the rate of drug release from a low mw polymer, sample 85(0.0308), was lower than that from polymers having both much higher mw and lactide content (Table 21).

The duration of the burst stage of release appeared to be approximately 2 days. The amount of drug released during that period, although tending to increase with the hydrophilicity of the matrix and ranging from 15.78 for the most hydrophobic 100(1.178) to 32% for the most hydrophillic 50(0.343) polymer (Figs. 46, 48 and 50), appeared primarily to be a function of formulation factors. The most influential formulation factor was the drug to polymer ratio (Fig. 45).

Sustained drug delivery using poly(lactide-co-glycolide) polymers has been pursued either by microencapsulation of the drug with the polymer or by melt extrusion of drug-polymer mixtures to produce implantable articles (e.g. small cylinders). In this work the use of poly(lactide-co-glycolide) heterogeneous matrix tablets as sustained release dosage forms was investigated. The manufacture of matrix tablets is a relatively simple and well known procedure which does not involve heating, as in melt extrusion, or solution of drug and polymer, as in microencapsulation. Consequently limitations arising from these processes such as polymer degradation, drug decomposition, protein denaturation by heat or problems associated with the solubility of polymer or drug in aqueous or organic solvents are avoided.

Drug release from microencapsulated products is relatively rapid due to their high specific surface area so that they are not normally suitable for long-term drug release applications. Biphasic drug release patterns have been reported with poly(lactide-co-glycolide) microcapsules (Beck *et al.*, 1983a). By contrast periods during which no drug or sub-effective amounts have been released may be observed with poly(lactide-co-glycolide) implants (Hutchinson and Furr, 1985; Sanders *et al.*, 1986). These periods were reduced, or eliminated, by employing rapidly degraded polymers, but this caused a decrease in the overall duration of the release. Consequently, the continuous release, occurring for the bulk of the process at an essentially constant rate, from poly(lactide-co-

glycolide) matrix tablets irrespective of the polymer used can be considered a significant improvement.

The rate of drug release from poly(lactide-co-glycolide) matrix tablets can be controlled by changing polymer characteristics such as the composition and mw, or by formulation factors such as the drug to polymer ratio, compaction pressure, and particle size. However, further research is required to investigate the significance of compaction pressure and particle size in conjunction with the polymer properties, on the long-term drug release . Each drug-polymer combination should be regarded as unique and the development of a sustained release dosage form based on poly(lactide-co-glycolide) polymers requires research involving the specific drug, the polymer and formulation parameters in order to find the optimum combination for the specific application. The choice of a particular poly(lactide-co-glycolide) polymer is particularly dictated by the intended lifetime of the preparation and, as a rule of thumb, the longer the intended lifetime the higher the lactide content and/or the mw of the polymer. The major problems that can be encountered in the preparation of matrix tablets using poly(lactide-co-glycolide) polymers are those associated with the flowability of polymer particles and the separation of the constituents of the drug-polymer mixture due to differences in particle density caused by the vibration of tableting machines. In such cases dry or wet granulation of the drug-polymer mixture might be useful. In wet granulation, using alcohol free water as granulating

liquid the polymer itself would function as binder due to its tacky nature. The investigation of the preparation and properties of poly(lactide-co-glycolide) tablets prepared by compacting granules might prove to be an interesting research field concerning the application of these polymers in controlled drug delivery.

The development of biotechnology and genetic engineering in recent years has generated increasing numbers of polypeptide and protein drugs and the controlled delivery of these heat and solution labile macromolecules using poly(lactide-co-glycolide) matrix tablets may be a useful alternative to their parenteral administration.

In conclusion, the feasibility of using spray dried poly(lactide-co-glycolide) polymers in the preparation of controlled release matrix tablets intended for subcutaneous or subdermal implantation has been demonstrated. Further research is required to fully elucidate the drug release mechanism from these matrix tablets. The investigation of release using drugs of similar aqueous solubility, but of different size, may be particularly useful in that respect as the diffusion through swollen polymers is very sensitive to the size of the diffusing molecules. Research involving specific types of drug where this formulation can be useful, such as contraceptive steroids, narcotic antagonists, antimalarial drugs, disulfiram, polypeptides, proteinic hormones and vaccines, and *in vivo* tests of the formulations produced, will also be required to establish the usefulness of this approach in the derivation of

prolonged therapeutic effects with a single dose of drugs administered by implantation.

6. APPENDICES

Appendix 1: Index of Figures

Appendix 2: Index of Tables

Appendix 3: References

Allcock, H.R., Kugel, R.L. and Valan, K.J., High Molecular weight poly(alkoxy and azyloxy phosphazenes). Inorg. Chem., 5(1966)1709-1715.

Allcock, H.R., and Moore, G.Y., PolymerizAtion and copolymerization of phenylhalogenocyclotriphosphazanes. Macromolecules, 8(1975)372-382.

Allcock, H.R. Schmutz, J.L. and Kosydar, K.M., A new route for poly(organophosphazene) synthesis. Polymerization, copolymerization and ring-ring equilibration of trifluoroethoxy and chloro-substituted cyclotriphosphazanes. Macromolecules, II(1978)179-186.

Allcock, H.R. and Austin, P.E., Schiff-base coupling of cyclic and high polymerIC phosphazenes to aldehydes and amines: chemotherapeutic models. Macromolecules, 14(1981)1616-1622.

Allcock, H.R. and Fuller, T.J., Phosphazene high polymers with steroidal side groups. Macromolecules, 13(1980)1338-1345.

Allcock, H.R., Austin, P.E. and Neenan, T.X., Phosphazene high polymers with bioactive substituent groups: prospective anaesthetic aminophosphazenes. Macromolecules, 15(1982_a)689-693.

Allcock, H.R., Neenan, T.X. and Kossa, W.C., Coupling of cyclic and high polymerIC aminoaryloxyphosphazenes to carboxyliC acids: prototypes for bioactive polymers. Macromolecules, 15(1982_b)693-697.

Allcock, H.R., Polyphosphazenes as new biomedical and bioactive materials. In Chasin, M. and Langer, R. (Eds), Biodegradable Polymers as Drug Delivery Systems, Marcel Decker, New York, 1990, pp.163-193.

Allen, R.W., O'Brien, J.P. and Allcock, H.R., Crystal and molecular structure of a platinum-cyclophosphazane complex cis-dichloro [octa (methylamino) cyclotetraphosphazene-N,N'] platinum (II). J. Am. Chem. Soc., 33(1977)3387-3391.

Anderson, L.C., Wise, D.L. and Howes, J.F., An injectable sustained release fertility control system. Contraception, 13(1976)375-384.

Baker, R.W. and Lonsdale, H.K., Controlled release: mechanisms and rates. In Tanquary, A.C. and Lacey, R.E. (Eds.), Controlled Release of Biologically Active Agents, Plenum Press, New York and London, 1974,pp.15-71.

Banga, A.K. and Chien, Y.W. Systemic delivery of therapeutic peptides and proteins. Int. J. Pharmac., 48(1988)15-50.

Beck, L.R., Cowsar, D.R., Lewis, D.H., Gibson, J.W. and Flowers, C.E., New long-acting injectable microcapsule contraceptive system. Am. J. Obstet. Gynecol., 135(1979)419-426.

Beck, L.R. and Tice, T.R., Poly(lactic acid) and Poly(lactic acid-co-glycolic acid) contraceptive delivery systems. In Mishell, D.R. (Ed.), Advances in Human Fertility and Reproductive Endocrinology, Raven Press, New York, 1983, pp.175-199.

Beck, L.R., Pope, V.Z., Flowers, C.E., Cowsar, D.R., Tice, T.R., Lewis, D.H., Dunn, R.L., Moore, A.B. and Gilley, R., Poly(dl-lactide-co-glycolide)/norethisterone microcapsules: an injectable biodegradable contraceptive. Biology of Reproduction 28(1983_a) 186-195.

Beck, L.R., Flowers, C.F., Pope, V.Z., Wilborn, W.H., and Tice, T.R., Clinical evaluation of an improved injectable microcapsule contraceptive system. Am. J. Obst. Gynecol., 147(1983_b)815-821.

Beck, L.R., Flowers, C.F., Cowsar, D.R. and Tanquary A.C., Active/passive immunization of the internal female reproductive organs. U.S. Patent, 4,732,763(1988).

Benagiano, G. and Gabelink, H.L., Biodegradable systems for the sustained release of fertility regulating agents. J. Steroid. Biochem., 11(1979)449-455.

Billmeyer, F.W., Textbook of Polymer Science, Wiley, New York, 1984.

Bissery, M.C., Valeriote, F. and Thies, C., *In vitro* lomustine release from small poly(β-hydroxybutyrate) and poly(dl-lactide) microspheres. Proc. Int. Symp. Control Rel. Bioact. Mater. , 11(1984)25-26.

Bissery, M.C., Valeriote, F. and Thies, C., Fate and effect of CCNU-loaded microspheres made of poly(d,l) lactide (PLA) or poly β-hydroxybutyrate (PHB) in mice. Proc. Int. Symp. Control. Rel. Bioact. Mater., 12(1985)181-182.

Bodmeier, R. and Chen, H., Preparation of biodegradable poly(+/-) lactide microparticles using a spray-drying technique. J. Pharm. Pharmacol., 40(1988)754-757.

Boerhinger Ingelheim, personal communication, 1989
Boswell, G.A. and Scribner, R.M., Polylactide-drug mixtures. U.S. Patent, 3,773,919(1973).

Brady, J.M., Cutright, D.E., Miller, A.R. and Battistone, G.C., Resorption rate, route of elimination and ultrastructure of the implant site of polylactic acid in the abdominal wall of the rat. J. Biomed. Mater. Res., 7(1973)155-166.

Brawn, D. and Kohl, P.R., Anionic solution polymerization of glycolide. Angew. Makromol. Chem. 139(1986)191-200.

Brekke, J.H., Olson, R.A.J., Scully, J.R.. and Osbon, D.B., Influence of polylactic acid mesh on the incidence of localized osteitis. Oral. Surg., 56(1983)240-245.

Brem, H., Ahn, H., Tamargo, R.J., Pinn, M. and Chasin, M., A biodegradable polymer for intracranial drug delivery. A radiological study. Abstracts of the Annual Meeting of the American Association of Neurological Surgeons, 1988_a, 349.

Brem, H., Tamargo, R.J., Pinn, M. and Chasin, M., Biocompatability of a BCNU-loaded biodegradable polymer. A toxicity study in primates. Abstracts of the American Association of Neurological Surgeons, 1988_b, 381.

Buckton, G., Contact angle, adsorption and wettability - a review with respect to powders. Powder Technol., 61(1990)237-249.

Cavalier, M., Benoit, J.P. and Thies, C., The formation and characterization of hydrocortisone-loaded poly([+/-]-lactide) microspheres. J. Pharm. Pharmacol., 38(1986)249-253.

Cha, Y. and Pitt, C.G., A one week subdermal delivery system for L-methadone based on biodegrade microcapsules. J. Controlled Release, 7,(1988)69-78

Chabot, F.. Vert, M. Chapelle, S. and Granger, P., Configurational structures of lactic acid stereocopolymers as determined by $^{13}C(^{1}H)$ n.m.r. Polymer, 24(1983)53-59.

Chasin, M., Lewis, D. and Langer, R., Polyanhydrides for controlled drug delivery. Biopharm. Manufact., 1(1988)33-46.

Chasin, M., Domb, A., Ron, E., Mathiowitz, E., Langer, R., Leong, K., Laurencin, C., Brem, H. and Grossman, S., Polyanhydrides as drug delivery systems. In Chasin, M. and Langer, R. (Eds.), Biodegradable Polymers as Drug Delivery Systems, Marcel Decker, New York, 1990, pp.43-70.

Chawla, A.S. and Chang, T.M.S., *In-vivo* degradation of poly(lactic acid) of different molecular weights. Biomat., Med. Dev. Art. Org., 13(1986)153-162.

Cherdron, H., Ohse, H. and Korte, F., Die polymerization von lactonen. Teil 1: Homopolymerization 4-, 6- and 7-gliedriger lactone mit kationischen initiatoren. Makromolekulare Chem. 56(1962)179-186.

Chujo, K., Kobayashi, H., Suzuki, J., Tokahra, S. and Tanabe, M., Ring opening polymerization of glycolide. Makromol. Chem., 100(1967)262-266.

Cohen, S., Yoshioka, T., Lucarelli, M., Hwang, L.H. and Langer, R., Controlled delivery systems for proteins based on poly(lactic/glycolic) acid microspheres. Pharm. Res., 8(1991)713-720.

Couvreur, P., Konte, B., Grislain, L., Roland, M. and Speicer, P., Toxicity of poly(alkyl cyanoacrylate) nanoparticles. II Doxorubicin-loaded nanoparticles. J. Pharm. Sci., 71(1982)790-792.

Cowsar, D.R., Tice, T.R., Gilley, R.M. and English, J.P., Poly(lactide-co-glycolide) microcapsules for controlled release of steroids. Methods Enzymol., 112(1985)101-116.

Craig, P.H., Williams, J.A., Davis, K.W., Magoun, A.D., Levy, A.J., Bogdansky, S. and Jones, J.P., A biologic comparison of polyglactin 910 and polyglycolic acid synthetic absorbable sutures. Surg. Gynecol. Obstet., 141(1975)1-10.

Cutright, D.E., Perer, B., Beasley, J.D., Larson, W.J. and Posey, W.R., Degradation rates of polymers and copolymers of polylactic and polyglycolic acids. Oral Surg., 37(1974)142-152

Deasy, P.B., Finan, M.P. and Meegan, M.J., Preparation and characterization of lactic/glycolic acid polymers and copolymers. J. Microencapsulation, 6(1989)369-378.

Dittrich, W. and Schulz, R.C., Kinetic und mechanismus der zingöffnenden polymerisation von l(-)-lactid. Ang. Makromol. Chem., 15(1971)109-126.

Domb, A. and Langer, R., Polyanhydrides. I. Preparation of high molecular weight polyanhydrides. J. Polym. Sci., 25(1987)3373-3386.

Dunn, R.L. Lewis, D.H. and Beck, L.R., Fibrous polymers for the delivery of contraceptive steroids to the female reproductive tract. In Lewis, D.H. (Ed.), Controlled Release of Pesticides and Pharmaceuticals, Plenum Press, New York and London 1981, pp.125-145.

Dunn, R.L., English, J.P., Stoner, W.C., Potter, A.G. and Perkins, B.H., Biodegradable fibres for the controlled release of tetracycline in treatment of periodontal disease. Proc. Int. Symp. Control. Rel. Bioact. Mater., 14(1987)259-260.

Dunn, R.L., English, J.P. Strobel, J.D., Cowsar, D.R. and Tice, T.R., Preparation and evaluation of lactide/glycolide copolymers for drug delivery. In Migliaresi, C., Nikolais, L., Giusti, P. and Chiellini, E. (Eds.), Polymers in Medicine III, Elsevier, Amsterdam, 1988, pp.149-160.

Edman, P., Ekman, B. and Sjoholm, I., Immobilization of proteins in microspheres of biodegradable polyacryl dextran. J. Pharm. Sci., 69(1980)838-842.

Eenink, M.J.D., Feijin, J., Olijslager, J., Albers, J.H.M., Rieke, J.C. and Greidanus, P.J., Biodegradable hollow fibres for the controlled release of hormones. J. Controlled Release, 6(1987)225-247.

Fell, J.T. and Newton, J.M., Determination of tablet strength by the diametral compression test. J. Pharm. Sci., 59(1970)688-691.

Fell, J.T. and Newton, J.M., Effect of particle size and speed of compaction on density changes in tablets of crystalline and spray-dried lactose. J. Pharm. Sci., 60(1971)1866-1869.

Filachione, E.M. and Fischer, C.H., Lactic acid condensation polymers: Preparation by batch and continuous methods. Industrial Engineering Chemistry 36(1944)223-228.

Florence, A.T., Hag, M.E. and Johnson, J.R., Interfacial properties of polymethyl a-cyanoacrylate and poly butyl cyanoacrylate. J. Pharm. Pharmacol., 28(1976)539-543.

Florence, A.T., Whatley, T.L. and Wood, D.A., Potentially biodegradable microcapsules with poly(alkyl-2-cyanoacrylate) membranes. J. Pharm. Pharmacol., 31(1979)422-424.

Fong, J.W., Processes for preparation of microspheres. U.S. Patent, 4,166,800(1979).

Frazza, E.J. and Schmitt, E.E., A new absorbable suture. J. Biomed. Mater. Res., 1(1971)43-58.

Fredericks, R.J., Melveger, A.J. and Dolegiewitz, L.J., Morphological and structural changes in a copolymer of glycolide and lactide occurring as a result of hydrolysis. J. Polym. Sci. Pol. Phys. Ed., 221(1984)57-56.

Ganderton, D and Selkirk, A.B., The effect of granule properties on the pore structure of tablets of sucrose and lactose. J. Pharm. Pharmacol., 22(1970)345-353.

Getter, L., Cutright, D.E., Bhaskar, S.N. and Augsburg, J.K., A biodegradable intraosseous appliance in the

treatment of mandibular fractures. J. Oral. Surg., 30(1972)344-348.

Gilding, D.K. and Reed, A.M., Biodegradable polymers for use in surgery - polyglycolic/poly(lactic acid) homo - and copolymers: 1. Polymer, 20(1979)1459-1464.

Gilding, D.K., Biodegradable polymers. Biocompat. Clin. Implant. Mater., 2(1981)209-232.

Gilley, R.M., Eldridge, J.H., Opitz, J.L., Hanne, L.K., Staas, J.K. and Tice, T.R., Development of secretory and systemic immunity followinG oral administration of microencapsulated antigens. Proc. Int. Symp. Control. Rel. Bioact. Mater., 15(1988)123-124.

Gould, P.L., Holland, S.J. and Tighe, B.J., Polymers for biodegradable medical devices IV. Hydroxybutyrate-valerate copolymers as non-disintegrating matrices for controlled release oral dosage forms. Int. J. Pharmac., 38(1987)231-237.

Graham, N.B. and Wood, D.A., Hydrogels and Biodegradable polymers for the controlled delivery of drugs. Polym. News., 8(1982)230-236.

Graham, N.B. and Wood, D.A., Polymeric inserts and implants for the controlled release of drugs. In Hastings, G.W. and Ducheyne, P. (Eds.), Macromolecular Biomaterials, CRC Press, Florida, 1984, pp.182-214.

Grassie, N., Murray, E.J. and Holmes, P.A., The thermal degradation of poly(D)-β-hydroxybutyric acid. Part 1 Identification and quantitative analysis of products. Polym. Degradation Stab., 6(1984)47-61.

Gresser, J.D., Wise, D.L., Beck, L.R. and Howes, J.F., Larger animal testing of an injectable sustained release fertility control system. Contraception 17(1978)253-266.

Gresser, J.D., Howes, J.F., Worth, D.F. and Howes, D.L., Polylactic/glycolic acid matrix systems for controlled delivery. In Wise, D.L. (Ed.), Biopolymeric Controlled Release Systems, CRC Press, Bocaraton, Florida, 1984, pp.35-49.

Grossman, S.A., Reinhard, C.S., Brem, H., Brundrette, R., Chasim, M., Tamargo, R. and Colvin, O.M., The intracerebral delivery of BCNU with surgically implanted biodegradable polymers: A quantitative autoradiographic study. Proc. Am. Soc. Clin. Oncol., 7(1988)84.

Guerrero, J., Rohovsky, M.W., Van der Westhuiren, B., Mellon, D. and Doddi, N., The use of mebendarole and levamisole in sustained release formulations. Janssen Res. Found. Ser., 2(1980)717-722.

Gumargalieve, K.Z., Moissev, Y.V., Daurota, T.T., Vozonkova, O.S. and Rozanova, I.B., Poly(caproamide)

degradation in rabbits and several model media. Biomaterials 1(1980)214-216.

Heckel, R.W., Density pressure relationships in powder compaction. Trans Metall. Soc. AIME., 221(1961a)671-675. 1961a

Heckel, R.W., An analysis of powder compaction phenomena. Trans. Metall. Soc. AIME, 221(1961b)1001-1008. 1961b

Hecquet, B., Chabot, F., Gonzalez, J.C.D., Fournier, C., Hilali, S., Cambier, L., Depadt, G. and Vert, M., *In vivo* sustained release of cisplatin from bioresorbable implants in mice. Anticancer Res., 6(1986)1251-1256.

Heller, J., Baker, R.W., Gale, R.M. and Rodin, J.O., Controlled drug release by polymer dissolution I. partial esters of maleic anhydride copolymers-properties and theory. J. App. Polym. Sci., 22(1978)1991-2009.

Heller, J. and Trescony, P.V., Controlled release by polymer dissolution II. Enzyme mediated delivery device. J. Pharm. Sci., 68(1979)919-921.

Heller, J., Penhale, D.W.H. and Helwing, R.F., Preparation of poly(ortho esters) by the reaction of ketene acetals and polyols. J. Polym. Sci.Polym. Lett. Ed.,18(1980)82-83.

Heller, J. and Baker, R.W., Theory and practice of controlled drug delivery from bioderodible polymers. In Baker, R.W. (Ed.), Controlled Release of Bioactive Materials, Academic Press, New York, 1980, pp.1-17.

Heller, J. Controlled release of biologically active compounds from bioderodible polymers. Biomaterials 1(1980)51-57.

Heller, J., Penhale, D.W.H., Fritzinger, B.K., Rose, J.E. and Helwing, R.F., Controlled release of contraceptive steroids from biodegradable poly(orthoesters). Contracept. Deliv. Syst., 4(1983)43-53.

Heller, J., Baker, R.W., Helwing, R.F. and Tuttle, M.E., Controlled release of water-soluble macromolecules from bioderodible hydrogels. Biomaterials, 4(1983)262-266.

Heller, J., Penhale, D.W.H., Fritzinger, B.K. and Ng, S.Y., Controlled release of contraceptive agents from poly(orthoesters). In Zatuchni, G.I., Goldsmith, A., Shelton, J.D. and Sciarra, J. (Eds.), Long Acting Contraceptive Delivery Systems, Harper and Row, Philadelphia, 1984, pp.113-128.

Heller, J., Fritzinger, B.K., Ng, S.Y. and Penhale, D.W.H., *In vitro* and *in vivo* release of levonorgestrel from poly(orthoesters) II. (cross linked polymers). Controlled Release, 1(1985)233-238.

Heller, J., Biodegradable polymers in controlled drug delivery. CRC Critical Reviews in Therapeutic Drug Carrier Systems, 1(1985)33-90.

Heller, J., Control of polymer surface erosion by the use of excipients. In Chielini, E., Migiaresi, P.C., Giusti, P. and Nikolais, L. (Eds.), Plenum Press, New York, 1986,pp.357-368.

Heller, J., Spacer, R.V., and Zentner, M., Poly(orthoesters). In Chasin, M. and Langer, R. (Eds.), Biodegradable polymers as drug delivery systems, Marcel Decker, New York, 1990, pp.121-161.

Higuchi, T., Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid materials. J. Pharm. Sci., 52(1963)1145-1149.

Holland, S.J., Tighe, B.J. and Gould, P.L., Polymers for biodegradable medical devices 1. The potential of polyesters as controlled macromolecular release systems. J. Controlled Release, 4(1986)155-180.

Holland, S.J., Jolly, A.M., Yasin, M. and Tighe, B.J., Polymers for biodegradable medical devices (2); hydroxybutyrate-hydroxyvalerate copolymers: hydrolytic degradation studies. Biomaterials, 8(1987)269-295.

Holmes, P.A., Application of PHB - a microbially produced biodegradable thermoplastic. Phys. Technol., 16(1985)32-36.

Hopfenberg, H.B., Controlled release from erodible slabs, cylinders and spheres. In Paul, D.R. and Harris, F.W. (Eds.), Controlled Release Polymeric Formulations, American Chemical Society, 1976, pp.26-32.

Hutchinson, F.G., Continuous release pharmaceutical compositions. EU. patent, 0,058,481,A1(1982).

Hutchinson, F.G. and Furr, B.J.A., Biodegradable polymers for the sustained release of peptides. Biochem. Soc. Trans., 13(1985)520-523.

Ibrahim, A., Couvreur, P., Roland, M. and Speiser, P., New magnetic drug carrier. J. Pharm. Pharmacol., 35(1989)59-61.

Ikada, Y., Hyon, S.H., Jamshidi, K., Higashi, S., Yamamuto, T., Katutani, Y. and Kitsugi, T., Release of antibiotics from composites of hydroxyapatite and poly(lactic acid). In Anderson, J.M. and Kim, S.W. (Eds.), Advances in Drug Delivery Systems, Elsevier, New York, 1986, pp.179-186.

Jackanicz, T.M., Nash, H.A., Wise, D.L. and Gregory, J.B., Polylactic acid as a biodegradable carrier for contraceptive steroids. Contraception, 8(1973)227-234.

Jacobson, H.W., Polymerization of cyclic carboxylic esters in the presence of a non polymerizable ester plasticizer. U.S. Patent, 3,498,957(1970).

Juni, K., Ogata, J., Nakano, M., Ichihara, T., Mori, K. and Akagi, M., Preparation and evaluation *in vitro* and *in vivo* of polylactic acid microspheres containing doxorubicin. Chem. Pharm. Bull., 33(1985)313-318.

Kaetsu, I., Yoshida, M., Asano, M., Yamanaka, H., Imai, K., Yuasa, H., Mashino, T., Suzuki, K., Katakai, R. and Oya, M., Biodegradable implant composites for local therapy. J. Controlled Release, 6(1987)249-263.

Kante, B., Couvreur, P., Dubois-Kracck, G., De Meester, C., Guiot, P., Roland, M., Mercier, M. and Speiser, P., Toxicity of poly(alkyl cyanoacrylate) nanoparticles 1. Free nanoparticles. J. Pharm. Sci., 71(1982)786-790.

Katz, A.R., Mukherjee, D.P., Kaganov, A.L. and Gordon, S., A new synthetic monofilament absorbable suture made from polytrimethylene carbonate. Surg. Gynacol. Obstet., 161(1985)213-222.

Kent, J.S., Sanders, L.M., Tice, T.R. and Lewis, D.H., Microencapsulation of the peptide nafarelin acetate for controlled release. In Zatuchni, G.I., Goldsmith, A., Shelton, J.D. and Sciana, J.J. (Eds.), Long-Acting Contraceptive Delivery Systems, Harper and Row, Philadelphia, 1984, pp.169-180.

Kitchell, J.P. and Wise, D.L., Poly(lactic/glycolic) biodegradable drug-polymer matrix systems. Methods Enzymol., 112(1985)436-448.

Klootwijk, A., Process for polymerization of lactides. U.S. Patent, 3,268,487(1966).

Kopecek, J., Soluble polymers in medicine. In Williams D.F. (Ed.), Systemic Aspects of Biocompatibility, CRC Press, Boca Raton, Florida, 1981, pp.159-180.

Korsatko, W., Wanbegg, B., Braunegg, G., Lafferty, R.M. and Stempfl, F., Poly D(-)-3-hydroxybuttersauce (PHB)-ein biologisch abbaubarer Azzneistofftrager zur liberationsverzogerung. 1. Mitt: Eintwicklung von parenteral applizierbaren matrix tabletten zur laugzeitabgabe von Arrheistoffen. Pharm. Ind., 45(1983)525-527.

Korsatko, W., Wabnegg, B., Tillian, H.M., Braunegg, G. and Lafferty, R.M., Poly D(-)-3-hydroxybuttersauce (PHB) - ein biologisch abbaubairer Azzneistofftrager zur liberationsverzogerung. 2.Mitt: Uber die biologische abbaubarkeit im tierischen organismus und die *in vitro - in vivo* korrelation der arzneistoffliberation aus parenteral applizierbaren matrix - retardtabletten. Pharm. Ind. 45(1983_b)1004-1007.

Kricheldorf, H.R., Joute, J.M. and Dunsing, R., The mechanism of cationic polymerization of β propiolactone and ϵ caprolactone. Makromol. Chem., 187(1986)771-785.

Kronenthal, R.L., Biodegradable polymers in medicine and surgery. In Kronenthal, R.L., User, Z. and Martin, E. (Eds.), Polymers in Medicine and Surgery, Plenum Press, New York, 1975, pp.119-137.

Kulkarni, R.K., Pani, K.C., Neman, C. and Leonard, F., Polylactic acid for surgical implants. Arch. Surgery., 93(1966)839-844.

Kulkarni, R.K., Moore, E.G., Hegyeli, A.F. and Leonard, F., Biodegradable poly(lactic acid) polymers. J. Biomed. Mater. Res., 5(1971)169-181.

Kwong, A.K., Chou, S., Sun, A.M., Sefton, M.V. and Goosen, M.F.A., *In vitro* and *in vivo* release of insulin from poly(lactic acid) microbeads and pellets. J. Controlled Release, 4(1986)47-62.

Laurencin, C., Koh, H.J., Neenan, T.X., Allcock, H.R. and Langer, R.S. Controlled release using a new bioerodible pholyphosphazene matrix system. J. Biomed. Mater. Res., 21(1987)1231-1246.

Lehman, R.A.W., Hayes, G.J., and Leonard, F., Toxicity of alkyl-2 cyanoacrylates. Arch. Surg., 93(1966)441-446.

Leonard, F., Kulkarni, R.K., Brandes, G., Nelson, J. and Cameron, J.J., Synthesis and degradation of poly(alkyl-a-cyanoacrylates). J. Appl. Polym. Sci., 10(1966)259-272.

Leonard, F., Kulkarni, R.K., Nelson, J. and Brandes, G., Tissue adhesives and homeostasis-inducing compounds: the alkyl cyanoacrylates. J. Biomed. Mater. Res., 1(1967)3-9.

Leong, K.W., Brott, B.C. and Langer, R., Bioerodible polyanhydrides as drug-carrier matrices I. Characterization degradation and release characteristics. J. Biomed. Mater. Res., 19(1985)941-955.

Leong, K.W., Kojt, J., Mathiowitz, E. and Langer, R., Polyanhydrides for controlled release of bioactive agents. Biomaterials, 7, (1986_a)364-371.

Leong, K.W., D'Amore, P., Marletta, M. and Langer, R., Bioerodible polyanhydrides as drug-carrier matrices: II. Biocompatability and chemical reactivity. J. Biomed. Mater. Res., 20(1986_b)51-64.

Lewis, D.H., Dappert, T.O., Meyers, W.E., Pritchett, G. and Suling, W.J., Sustained release of antibiotics from biodegradable microcapsules. Proc. Int. Symp. Control. Rel. Bioact. Mater., 7(1980)129-131.

Lewis, D.H. and Tice, T.R., Polymeric considerations in the design of microencapsulated contraceptive steroids in Zattuchni, G.I. (Ed.), Long Acting Contraceptive Delivery Systems, Harper and Row, Philadelphia, 1983, pp.77-85.

Lewis, D.H., Beck, L.R., Forman, T.D., Manck, T.A. and Pope, V.Z., Reproducibility studies on microencapsulation of steroids in biodegradable polymers. Proc. Int. Symp. Control. Rel. Bioact. Mater., 15(1988)266-267.

Lewis, D.H., Controlled release of bioactive agents for lactide/glycolide polymers. In Chasim, M. and Langer, R. (Eds.), Biodegradable Polymers as Drug Delivery Systems, Marcel Decker, New York, 1990, pp.1-41.

Lowe, C.E., Preparation of high molecular weight polyhydroxyacetic ester. U.S. Patent, 2,668,162(1954).

Makino, K., Arakowa, M. and Kondo, T., Preparation and *in vitro* degradation properties of polylactide microcapsules. Chem. Pharm. Bull., 33(1985)1195-1201.

Makino, K., Oshima, H. and Kondo, T., Transfer of protons from bulk solution to the surface of poly(L-lactide) microcapsules. J. Microencapsulation, 3(1986_a)195-202.

Makino, K., Oshima, H. and Kondo, T., Mechanism of hydrolytic degradation of poly(L-lactide) microcapsules: effects of pH, ionic strength and buffer concentration. J. Microencapsulation, 3(1986_b)203-212.

Marcotte, N., Polk, A. and Goosen, M.F.A., Kinetics of protein diffusion from a poly(d,l-lactide) reservoir system. J. Pharm. Sci., 79(1990)407-410.

Mason, D.W., McRae-Degueurce, A., Dillon, D.L., Gilley, R.M. and Tice, T.R., Biodegradable poly(dl-lactide-co-glycolide) microcapsules for the controlled release of catecholamines to the CNS. Proc. Int. Symp. Control. Rel. Bioact. Mater., 15(1988)270-271.

Masters, K., Spray drying handbook, Goodwin Ltd., London, 1985,p10 and 32.

Mathiowitz, E., Leong, K. and Langer, R., Macromolecular drug release from biodegradable polyanhydride microspheres. Proc. Int. Symp. Control. Rel. Bioact. Mater., 12(1985)183-184.

Mathiowitz, E. and Langer, R., Polyanhydride microspheres as drug carriers I. Hot-melt microencapsulation. J. Controlled Release, 5(1987)13-22.

Maulding, H.V., Prolonged delivery of peptides by microcapsules. J. Controlled Release, 6(1987)167-176.

Merritt, J.C., Chapman, L. and Rabb, M., Polyglycolic acid suture in strabismus surgery. Arch, Opthalmol., 91(1979)433-440.

Miller, R.A., Brady, J.M. and Cutright, D.E., Degradation rates of oral resorbable implants (polylactates and polyglycolates): rate modification with changes in PLA/PGA copolymer ratios. J. Biomed. Mater. Res., 11(1977)711-719.

Moiseev, Y.V., Daurota, T.T., Voronkova, O.S., Gumargalieve, K.Z. and Privalova, L.G., The specificity of polymer degradation in the living body. J. Polym. Sci. (Polym. Symp.) 66(1979)269-281.

Mungiu, C., Gogalniceanu, D., Leibovici, M. and Negulescu, I., On the medical use of cyanoacrylic esters: toxicity of pure n-butyl-a-cyanoacrylate. J. Polym. Sci. (Polym. Symp.) 66(1979)189-193.

Nuwayser, E.S. and Deroo, D.J., Microencapsulation with microfluidized bed. Proc. Int. Symp. Control. Rel. Bioact. Mater., 14(1987)304-305.

Nuwayser, E.S., Gay, M.H., DeRoom D.J. and Blaskovish, D.D., Sustained release injectable naltrexone microspheres. Proc. Int. Symp. Control. Rel. Bioact. Mater., 15(1988)201-202.

Ogawa, Y., Yamamoto, M., Okada, H., Yashiki, T. and Shimamoto, T., A new technique to efficiently entrap Leuprolide acetate into microcapsules of polylactic acid or copoly(lactic/glycolic) acid. Chem. Pharm. Bull., 36(1988$_a$)1095-1103.

Ogawa, Y., Yamamoto, M., Takada, S., Okada, H. and Shimamoto, T., Controlled release of Leuprolide acetate from polylactic acid or copoly(lactic/glycolic) acid microcapsules: influence of molecular weight and copolymer ratio of polymer. Chem. Pharm. Bull., 36(1988$_b$) 1502-1507.

Ogawa, Y., Okada, H., Yamamoto, M. and Shimamoto, T., *In vivo* release profiles of Leuprolide acetate from microcapsules prepared with polylactic acids or copoly(lactic/glycolic) acids and *in vivo* degradation of these polymers. Chem. Pharm. Bull., 36(1988_c)2576-2581.

Omelczuk, M.O., Chang, K.T. and McGinity, J.W., Effect of thermal treatment on the physical-mechanical and dissolution properties of compacts containing biodegradable polymers. 9th Pharmaceutical Technology Conference, Veldhoven, The Netherlands, 1990, vol.1, pp.28-44.

Petersen, R.V., Anderson, C.G., Fang, S.M., Gregonis, D.E., Kim. S.W., Feijen, J., Anderson, J.M., and Mitra, S., Controlled release of progestins from poly(a-amino acid) carriers. In Baker, R.W. (Ed.), Controlled Release of Bioactive Materials, Academic Press, New York, 1980,45-60.

Phillips, M. and Gresser, J.D., Sustained-Release characteristics of a new implantable formulation of disulfiram. J. Pharm. Sci., 73(1984)1218-1221.

Pitt, C.G., Gratzl, M.M., Jeffcoat, A.R., Zweidinger, R. and Schindler, A., Sustained drug delivery systems II: factors affecting release rates from poly(ϵ-caprolactone) and related biodegradable polyesters. J. Pharm. Sci., 68(1979)(1534-1538).

Pitt. C.G., Marks, T.A. and Schindler, A., Biodegradable drug delivery systems based on aliphatic polyesters: application to contraceptives and narcotic antagonists. In Baker, R.W. (Ed.), Controlled Release of Bioactive Material, Academic Press, 1980, pp.19-43.

Pitt, C.G., Chasalow, F.I., Hibionana, Y.M., Klimas, D.M. and Schindler, A., Aliphatic polyesters I. The degradation of poly(caprolactone) *in vivo*. J. Appl. Polym. Sci., 26(1981_a)3779-3787.

Pitt, C.G., Gratzl, M.M., Kimmel, G.L., Surles, J. and Schindler, A., Aliphatic polyesters II. The degradation of poly(dl-lactide), poly(ϵ-caprolactone), and their copolymers *in vivo*. Biomaterials, 2(1981_b)215-220.

Pitt, C.G. and Schindler, A., Capronor: A biodegradable system for levonorgestrel. In Zatuchni, G.I., Goldsmith, A., Shelton, J.D. and Sciarra, J.J. (Eds.), Long-Acting Contraceptive Delivery Systems, Harper and Row, Philadelphia, 1984, pp.48-63.

Pitt, C.G. and Gu, Z., Modification of the rates of chain cleavage of poly(ϵ-caprolactone) and related polyesters in the solid state. J. Controlled Release, 4, (1987)283-292.

Pitt, C.G., Cha, Y., Henderen, R.W, Holloman, M. and Schindler, A., Manipulation of the permeability and degradability of polymers. Proc. Int. Symp. Control. Rel. Bioact. Mater., 14(1987)75-76.

Pitt, C.G., Poly(ε-caprolactone) and its copolymers. In Chasim, M and Langer, R. (Eds.), Biodegradable Polymers as Drug Delivery Systems, Marcel Decker, New York, 1990_a, pp.70-120.

Pitt, C.G., The controlled parenteral delivery of polypeptides and proteins. Int. J. Pharmac, $59(1990_b)$173-196.

Pouton, C.W., Kennedy, J.E., Natarianni, L.J. and Gould, P.L., Biocompatibility of poly-βhydroxybutyrate and related copolymers. Proc. Int. Symp. Control. Rel. Bioact. Mater., 15(1988)179-180.

Quackenbos, H.M., Relation between intrinsic viscosity and molecular weight. J. Appl. Polym. Sci., 25(1980)1435-1442.

Rak, J., Ford, J.L., Rostron, C. and Walters, R., The preparation and characterization of poly(d,l-lactic-acid) for use as biodegradable drug carrier. Pharm. Acta. Helv., 60(1985)162-169.

Rankell, A. and Lieberman, H.A., Drying. In Lachman, L., Lieberman, H.A. and Kanig, J.L. (Eds.). The Theory and Practice of Industrial Pharmacy, Lea and Febiger, Philadelphia, 1976(2nd edition), pp.503.524.

Ratcliffe, J.H., Hunneyball, I.M., Smith, A., Wilson, C.G and Davis, S.S., Preparation and evaluation of biodegradable polymeric systems for the intra-articular delivery of drugs. J. Pharm. Pharmacol., 36(1984)431-436.

Ravens, D.A.S. and Ward, I.M., Chemical reactivity of polyethylene terephthalate. Hydrolysis and esterification reactions in the solid phase. Trans. Farrad, Soc., 57(1961)150-159.

Reed, A.M. and Gilding, D.K., Biodegradable polymers for use in surgery - poly(glycolic/poly(lactic acid) homo- and copolymers. 2: *In vitro* degradation. Polymer, 22(1981)494-498.

Roberts, R.J. and Rowe, R.C., The compaction of pharmaceutical and other materials, a pragmatic approach. Chem. Eng. Sci., 42(1987)903-911.

Rokkanen, P., Vainionpaa, S., Tormala, P., Kilpikari, J., Bostman, O., Vihtonen, K., Laiho,. and Tomminmaki, M., Biodegradable implants in fracture fixation: early results of treatment of fractures on the ankle. The Lancet, June 22(1985)1422-1424.

Rowland, G.R., O'Neill, G.J. and Davies, D.A.L., Suppression of tumour growth in mice by a drug antibody conjugate using a novel approach to linkages. Nature, 255(1975)487-488.

Rue, P.J. and Rees, J.E., Limitations of Heckel relation for predicting powder compaction mechanisms. J. Pharm. Pharmacol., 30(1978)642-643.

Sanders, L.M., Kent, J.S., McRae, G.I., Vickery, B.H., Tice, T.R. and Lewis, D.H., Controlled release of luteinizing hormone-releasing hormone analogue from poly(d,l-lactide-co-glycolide) microspheres. J. Pharm. Sci., 73(1984)1294-1297

Sanders, L.M., Kell, B.A. and Whitehead, G.W., Prolonged controlled-release of Nafarelin, a luteinizing hormone-releasing analogue from biodegradable polymeric implants: Influence of composition and molecular weight of polymer. J. Pharm. Sci., 75(1986)356-360.

Sanders, L., Burns, R., Vitale, K. and Hoffman, R., Clinical performance of nafarelin controlled release injectable: influence of formulation parameters on release kinetics and duration of efficacy. Proc. Int. Symp. Control. Rel. Bioact. Mater., 15(1988)62-63.

Schindler, A., Jeffcoat, R., Kimmel, G.L., Pitt, C.G., Wall, M.E. and Zweidigger, R., Biodegradable polymers for sustained drug delivery. In Pearce, E.M. and Schaefgen, J.R., (Eds.), Contemporary Topics in Polymer Science, Plenum Press, New York, 1977, pp.252-286.

Schindler, A. and Harper, D., Polylactide. II. Viscosity-molecular weight relationships and unperturbed chain dimensions. J. Polym. Sci., Polym. Chem. Ed., 17(1979)2593-2599.

Schindler, A., Porous bioabsorbable polyesters as controlled-release reservoirs for high molecular weight drugs, EU. Patent application, 2,237,008, May 1987.

Schmitt, E.E., Epstein, M. and Polistina, R.A., Process for polymerizing a glycolide. U.S. Patent, 3,442,871(1969).

Schwope, A.D., Wise, D.L. and Howes, J.F., Lactic/glycolic acid polymers as narcotic antagonist delivery systems. Life Sci., 17(1975)1877-1886.

Shalaby, S.W. and Jamiolkowski, D.D., Absorbable pharmaceutical compositions based on isomorphic copolyoxalates. U.S. Patent, 4,130,639(1978).

Sidman, K.R., Schwope, A.D., Steber, W.D., Rudolph, S.E and Poulin, S.B., Use of synthetic polypeptides for biodegradable drug delivery systems. Polym. prepr., 20(1979)27-31.

Sidman, K.R., Schwope, A.D., Steber, W.D., Rudolph, S.E. and Poulin, S.B., Biodegradable implantable sustained release systems based on glutamic acid copolymers. J. Membr. Sci., 7(1980)277-291.

Sidman, K.R., Steber, W.D., Schwope, A.D. and Schnaper, G.R., Controlled release of macromolecules and pharmaceuticals from synthetic polypeptides based on glutamic acid. Biopolymers, 22(1983)547-556.

Siemann, V., Densitometric determination of the solubility parameters of biodegradable polyesters. Proc. Int. Symp. Control. Rel. Bioact. Mater., 12(1985)53-54.

Singh, M., Taforo, T., Laderman, K. and Rana, S., Release of a model protein from biodegradable poly(dl-lactide-co-glycolide) microcapsules. Proc. Int. Symp. Control. Rel. Bioact. Mater., 15(1988)456-457.

Singh, M., Singh, A. and Talivar, G.P., Controlled delivery of diphtheria toxoid using biodegradable poly(d,l-lactide) microcapsules. Pharm. Res., 8(1991)958-961.

Smith, A. and Hunneyball, L.M., Evaluation of poly(lactic acid) as a biodegradable drug delivery system for parenteral administration. Int. J. Pharm., 30(1986)215-220.

Solomon, O.F. and Ciuta, I.Z., Determination de la viscosité intrisèque de solutions de polymers par une simple détermination de la viscosité. J. Appl. Polym. Sci., 6(1962)683-686.

Sparer, R.V., Chung, S., Ringeisen, C.D. and Himmelstein, K.J., Controlled release from erodible poly(orthoester) drug delivery system. J. Controlled Release, 1(1989)23-32.

Spenlehouer, G., Benoit, J.P. and Veitlard, M., Formation and characterization of poly(d,l-lactide) microspheres for chemoemobilization. J. Pharm. Sci., 25(1986)750-755.

Spenlehouer, G., Vert, M., Benoit, J.P., Chabot, F. and Veillard, M., Biodegradable cisplatin microspheres prepared by the solvent evaporation method: Morphology and release characteristics. J. Controlled Release, 7(1988)217-229.

Spilizewski, K.L., Marchant, R.E., Hamlin, C.R., Anderson, J.M., Tice, T.R., Dappert, T.O. and Meyers, W.E., The effect of hydrocortisone acetate loaded poly(d,l,-lactide) films on the inflammatory response. In Anderson, J.M. and Kim, S.W. (Eds.), Advances in Drug Delivery, Elsevier, New York, 1986, pp.197-203.

Strobel, J.D., Laughin, T.J., Ostroy, F., Lilly, M.D., Perkins, B.H and Dunn, R.L., Controlled release systems for anticancer agents. Proc. Int. Symp. Control. Rel. Bioact. Mater., 14(1987)261-262.

Suzuki, J. and Price, J.C., Microencapsulation and dissolution properties of α neuroleptic in a biodegradable polymer, poly(d,l-lactide). J. Pharm. Sci., 74(1985)21-24.

The United States Pharmacopoeia XXII, Mack Publishing Co., Easton, PA, 1990, p.1578.

Tice, T.R., Lewis, D.H., Dunn, R.L., Meyers, W.E., Casper, R.A. and Cowsar, D.R., Biodegradation of microcapsules and biomedical devices prepared with resorbable polyesters. Proc. Int. Symp. Control. Rel. Bioact. Mater., 9(1982)21-25.

Tice, T.R., and Lewis, D.H., Microencapsulation process. U.S. Patent, 4,389,330(1983).

Tice, T.R., Rowe, C.E. and Setterstrom, J.A., Development of microencapsulated antibiotics for topical administration to wounds. Proc. Int. Symp. Control. Rel,. Bioact. Mater., II(1984)61-62.

Tice, T.R. and Cowsar, D.R., Biodegradable controlled release parenteral systems. Pharm. Tech., 8(1984)26-35.

Tice, T.R., Lewis, D.H., Cowsar, D.R. and Beck, L.R., Injectable, long acting microparticle formulation for the delivery of anti-inflammatory agents. U.S. Patent, 4,542,025(1985).

Tice, T.R., Rowe, C.E., Gilley, R.M., Setterstrom, J.A. and Mirth, D.D., Development of microencapsulated antibiotics for topical administration. Proc. Int. Symp. Control. Rel. Bioact. Mater., 13(1986)163-170.

Tice, T.R, Pledger, K.L. and Gilley, R.M., Microencapsulation of DNA and/or RNA, especially for stimulation of interferon production. EU. Patent Application, 248,531,1987.

Tsai, D.C., Howard, S.A., Hogan, T.F., Malangu, C.J., Kandzari, S.J. and Ma, J.K., Preparation and *in vitro* evaluation of polylactic acid-mitomycin c microcapsules. J. Microencapsul., 3(1986)181-193.

Tsakala, M., Gillard, J. and Rowland, M., Pyrimethamine sustained release system based on bioresorbable polyesters for chemoprophylaxis of rodent malaria. J. Controlled Release, 5(1988)233-242.

Tsuruta, T., Matsura, K. and Inone, S., Preparation of some polyesters by organometallic-catalyzed ring opening polymerization. Makromol. Chem., 75(1964)211-214.

Tunc, D.C., Rohovsky, M.W., Jadah, B., Lechman, W.B., Strongwater, A. and Kummer, F., Evaluation of body absorbable bone fixation devices. Polym. Mater. Sci. Eng., 53(1985)502-504.

Vert, M., Chabot, F., Leray, J. and Christel, P., Stereoregular bioresorbable polyester for orthopaedic surgery. Makromol. Chem., Suppl.5(1981)31-41.

Vezin, W.R. and Florence, A.T., *In vitro* heterogenous degradation of poly(n-alkyl-a-cyanoacrylates). J. Biomed. Mater. Res., 14(1980)93-106.

Williams, D.F. and Mort, E., Enzyme-accelerated hydrolysis of poly(glycolic acid). J. Bioeng., 1(1977)231-238.

Williams, D.F., Enzyme hydrolysis of polylactic acid. Eng. Med. 10(1981)5-8.

Williams, D.F. Biodegradation of surgical polymers. J. Mater. Sci., 17(1982)1233-1246.

Williams, D.L., Nuwayser, E.S., Greeden, D.E. and Gay, M.H., Microencapsulated local anaesthetics. Proc. Int. Symp. Control. Rel. Bioact. Mater., 11(1984)69-70.

Wise, D.L., McCormick, G.J., Willet, G.P. and Anderson L.C., Sustained release of an antimalarial drug using a copolymer of glycolic/lactic acid. Life Sci.,19(1976)867-873.

Wise, D.L., Gregory, J.B., Newborne, D.M., Bartholow, L.C. and Stanbury, J.B., Results on biodegradable cylindrical subdermal implants for fertility control. In Kostelnik, R.J. (Ed.), Polymeric Delivery Systems, Gordon and Breach, New York, 1978_a, pp.121-136.

Wise, D.L., McCormic, G.J., Willet, G.P., Anderson, L.C. and Howes, J.F., Sustained release of sulphathiazine. J. Pharm. Pharmacol., $30(1978_b)$686-689.

Wise, D.L., Fellman, T.D., Sanderson, J.E. and Wentworth, R.L., Lactic/Glycolic acid polymers. In Gregoriadis, G. (Ed.), Drug Carriers in Biology and Medicine. Academic Press, New York, 1979_a, pp.237-270.

Wise, D.L., Gresser, J.D. and McCormick, G.J., Sustained release of a dual antimalarial drug. J. Pharm. Pharmacol., $31(1979_b)$201-204.

Wise, D.L., Rosenkrantz, H., Gregory, J.B. and Esber, H., Long-term controlled delivery of levonorgestrel in rats by means of small biodegradable cylinders. J. Pharm. Pharmacol., 32(1980)399-403.

Woodland, J.H.R, Yolles, S., Blake, D.A., Helrich, M. and Meyer, F.J., Long Acting delivery systems for narcotic antagonists. 1. J. Med. Chem., 16(1973)897-901.

Yolles, S., Eldridge, J.E. and Woodland, J.H.R., Sustained delivery of drugs from polymer/drug mixtures. Polym. News, 1(1970)9.

Yolles, S., Controlled release of biologically active agents. In Kronenthal, R.L., User, Z. and Martin, E. (Eds.), Polymers in Medicine and surgery. Plenum Press, New York, 1975, pp.245-261.

Yolles, S., Morton, J.F. and Rosenberg, B., Timed-release depot for anti cancer agents. II Acta Pharm. Suec., 15(1978)382-388.

York, P., and Pilpel, N., The Tensile strength and compression behaviour of lactose, four fatty acids, and their mixtures in relation to tableting. J. Pharm. Pharmacol., 25S(1973)1P-11P.